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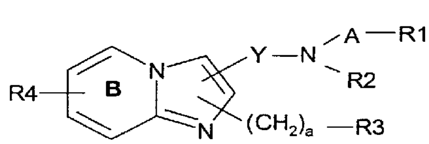
(54) Title: ANTAGONISTS OF GONADOTROPIN RELEASING HORMONE



(I)

(57) Abstract: The present invention relates to compounds of formula I which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds.

ANTAGONISTS OF GONADOTROPIN RELEASING HORMONE

The present invention relates to compounds which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds.

BACKGROUND TO THE INVENTION

Gonadotropin releasing hormone (GnRH) is a decapeptide that is secreted by the hypothalamus into the hypophyseal portal circulation in response to neural and/or chemical stimuli, causing the biosynthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary. GnRH is also known by other names, including gonadoliberin, LH releasing hormone (LHRH), FSH releasing hormone (FSH RH) and LH/FSH releasing factor (LH/FSH RF).

GnRH plays an important role in regulating the action of LH and FSH (by regulation of their levels), and thus has a role in regulating the levels of gonadal steroids in both sexes, including the sex hormones progesterone, oestrogens and androgens. More discussion of GnRH can be found in WO 98/5519 and WO 97/14697, the disclosures of which are incorporated herein by reference.

It is believed that several diseases would benefit from the regulation of GnRH activity, in particular by antagonising such activity. These include sex hormone related conditions such as sex hormone dependent cancer, benign prostatic hypertrophy and myoma of the uterus. Examples of sex hormone dependent cancers are prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

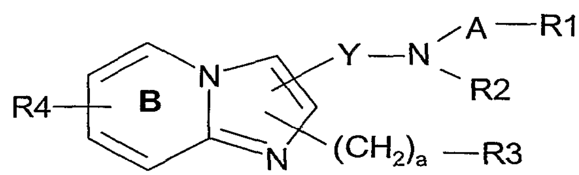
The following disclose compounds purported to act as GnRH antagonists: WO 97/44041, WO 98/5519, WO 99/51596 and WO 97/14697.

It would be desirable to provide further compounds, such compounds being GnRH antagonists.

SUMMARY OF THE INVENTION

The present invention accordingly provides a compound of formula **I** or a pharmaceutically acceptable salt or solvate thereof

I



wherein:-

For R1 and R2, either:-

(i) R1= -C(X)NR5R6; -C(=NCN)NR5R6; -C(=CHNO$_2$)NR5R6; an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure containing from 1 to 5 heteroatoms independently selected from O, N and S; optionally substituted C1 to C8 alkyl; optionally substituted aryl; or optionally substituted aralkyl, where the alkyl moiety is C1 to C8;

R2 = H; optionally substituted C1 to C8 alkyl; optionally substituted aryl; optionally substituted aralkyl; -R7-R8, wherein R7 represents optionally substituted C1 to C8 alkyl and R8 represents an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure containing from 1 to 5 heteroatoms

independently selected from O, N and S; optionally substituted C2 to C12 alkenyl; or optionally substituted alkenylaryl, wherein the alkenyl moiety is C2 to C12; and

A = a single bond; optionally substituted C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; or –R-Ar-R'-, where R and R' are independently selected from a bond, optionally substituted C1 to C8 alkylene and a C2 to C12 group having at least one alkene double bond; and Ar represents optionally substituted aryl.

(ii) the structure N-R1R2 represents a 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S and optionally fused to a C5 to C10 ring structure, N-R1R2 being optionally substituted;

For R3 and R4, either R3 is selected from (iii) and R4 selected from (iv); or R3 is selected from (iv) and R4 selected from (iii):-

(iii) H; -ZR9, halogen; -ZC(O)NR9R10; -ZC(O)OR9; -ZC(O)SR9; -ZC(O)R9; C(R9)=N-OR10; -ZNR9C(O)NR10R11; -ZNR9SO_2R10; -ZSO_2R9R10; -ZCR9$(CN)_2$; -ZN(R9)CN; or an optionally substituted 3- to 6-membered heterocyclic ring containing from 1 to 3 heteroatoms independently selected from O, N and S;

(iv) -Z'-M, wherein

M represents a mono- or bi-cyclic aromatic ring structure optionally having at least one substituent selected from CN; NR12R13; an optionally substituted C1 to C8 alkyl; optionally substituted C1 to C8 alkoxy; halogen; $(CH_2)_b$-C(O)NR12R13; NR12-C(O)NR13R14; $(CH_2)_b$-SO_2NR12R13; NR12C(O)R13; NR12SO_2R13; $(CH_2)_b$OH; NR12CN; and CR12$(CN)_2$;

Wherein each R5, R6, R10, R11, R12, R13 and R14 is independently selected from H; optionally substituted C1 to C8 alkyl and optionally substituted aryl;

R9 is selected from H; optionally substituted C1 to C8 alkyl; optionally substituted aryl; -R-Ar, where R represents C1 to C8 alkylene and Ar represents optionally substituted aryl; and optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S;

X = O; S; or NR''', where R''' is H or C1 to C8 alkyl;

Y = a bond; C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; or a C2 to C12 group having at least one alkyne triple bond;

Z = a bond; C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; a C2 to C12 group having at least one alkyne triple bond; or -CR(R'), where R and R' are independently selected from H, CN, halogen, C1 to C8 alkyl, CH_2F, CHF_2, and C3 to C8 cycloalkyl;

Z' = a bond; C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; a C2 to C12 group having at least one alkyne triple bond; or -CR(R'), where R and R' are independently selected from H, CN, halogen, C1 to C8 alkyl, CH_2F, CHF_2, and C3 to C8 cycloalkyl;

a = zero or an integer from 1 to 8;

each b independently represents zero or an integer from 1 to 8;

Wherein ring **B** is optionally further substituted.

The present invention also provides a pharmaceutical formulation comprising such a compound and a pharmaceutically acceptable diluent or carrier.

Furthermore, the present invention provides the following uses of the compound:-

(a) Use in the manufacture of a composition, for antagonising gonadotropin releasing hormone activity.

(b) Use in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinising hormone by the pituitary gland of the patient.

(c) Use in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient.

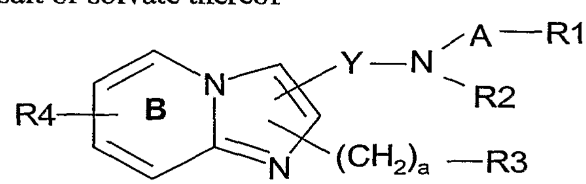
The present invention also relates to a method of antagonising gonadotropin releasing hormone activity in a patient, comprising administering the compound to the patient.

In addition, the invention provides a process of producing the compound.

DETAILED DESCRIPTION OF THE INVENTION

As discussed above, the present invention provides a compound of formula **I** or a pharmaceutically acceptable salt or solvate thereof

I



wherein:-

For R1 and R2, either option (i) or (ii) applies:-

(i) R1= -C(X)NR5R6; -C(=NCN)NR5R6; -C(=$CHNO_2$)NR5R6; an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure (preferably, a 5- or 6-membered monocyclic ring) containing from 1 to 5 (preferably, 1 or 2) heteroatoms independently selected from O, N and S; optionally substituted C1 to C8 alkyl (preferably, C1 to C4 alkyl, and most preferably methyl); optionally substituted aryl (preferably optionally substituted phenyl); or optionally substituted aralkyl, where the alkyl moiety is C1 to C8 (preferably, C1 to C4 alkyl, and most preferably methyl) and the aryl moiety is preferably phenyl;

R2 = H (which is the most preferred for R2); optionally substituted C1 to C8 alkyl (preferably, C1 to C4 alkyl, and most preferably methyl); optionally substituted aryl (eg, phenyl); optionally substituted aralkyl (eg, phenylalkyl, where the alkyl is C1 to C8, preferably C1 to C4 alkyl, and most preferably methyl); -R7-R8, wherein R7 represents optionally substituted C1 to C8 alkyl (preferably, C1 to C4 alkyl, and most preferably methyl) and R8 represents an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure (preferably, a 5- or 6-membered monocyclic ring) containing from 1 to 5 (eg, 1 or 2) heteroatoms independently selected from O, N and S; optionally substituted C2 to C12 alkenyl (preferably, C2 to C10, more preferably C2 to C6 alkenyl); or optionally substituted alkenylaryl, wherein the alkenyl moiety is C2 to C12 (preferably, C2 to C10, more preferably C2 to C6 alkenyl), and preferably the aryl is phenyl; and

A = a single bond; optionally substituted C1 to C8 alkylene (preferably, C1 to C4 alkylene, and most preferably methylene); a C2 to C12 group having at least one alkene double bond; or –R-Ar-R'-, where R and R' are independently selected from a bond, optionally substituted C1 to C8 alkylene (preferably, C1 to C4 alkylene, and most preferably methylene) and a C2 to C12 group having at least one alkene double bond; and Ar represents optionally substituted aryl (eg, optionally substituted phenyl).

In the definition of A, where a C2 to C12 group having at least one alkene double bond is mentioned, this may have from 1 to 11 (more preferably 1 to 8) alkene double bonds (eg, 1, 2 or 3 alkene double bonds). The group can be straight chain or branched.

Option (ii) is as follows:-

(ii) the structure N-R1R2 represents a 3- to 8- membered heterocyclic ring (preferably, a 5- or 6-membered monocyclic ring) optionally containing from 1 to 3 (eg, 1) further heteroatoms independently selected from O, N and S and optionally fused to a C4 to C10 (preferably, C4, C5 or C6) ring structure (eg, a carbocyclic ring structure or a ring structure comprising a heteroatom selected from O, N and S), N-R1R2 being optionally substituted.

Preferably, R1 is represented by option (i) and X represents S. In addition, or alternatively, preferably, R1 is represented by option (i) and R5 and R6 each represent H.

In one embodiment, R1 represents optionally substituted pyridyl, eg 2-pyridyl. One example of suitable substitution of the pyridyl is at the 6-position, eg with –NRR', wherein R and R' are independently selected from H and C1 to C8 alkyl (preferably, C1 to C4 alkyl, and most preferably methyl).

In another embodiment, R1 represents optionally substituted phenyl and R2 represents H, A being a single bond or methylene.

In a further embodiment, R1 represents –(C(=NCN)NH(CH_3) and R2 represents H, A being a single bond or methylene.

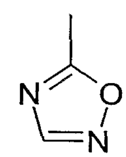
In yet another embodiment, R1 represents optionally substituted phenyl and R2 represents –CH_2-phenyl, A being a single bond or methylene.

For R3 and R4, either R3 is selected from (iii) and R4 selected from (iv); or R3 is selected from (iv) and R4 selected from (iii):-

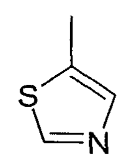
(iii) H; -ZR9 (representing, eg, methyl), halogen (eg F, Br or Cl); -ZC(O)NR9R10 (eg, where R9 and R10 are each ethyl); -ZC(O)OR9 (eg, where R9 is ethyl); -ZC(O)SR9; -ZC(O)R9 (preferably where R9 represents optionally substituted phenyl or *i*-propyl); C(R9)=N-OR10 (preferably where R10 represents optionally substituted methyl); -ZNR9C(O)NR10R11(preferably, NHC(O)NHR11); -ZNR9SO_2R10; -ZSO_2R9R10; -ZCR9$(CN)_2$; -ZN(R9)CN; or an optionally substituted 3- to 6-membered heterocyclic ring containing from 1 to 3 heteroatoms independently selected from O, N and S.

Preferably, the heterocyclic ring is a substituent of formula **II** or **III**:-

II



III



Option (iv) is as follows:-

(iv) -Z'-M, wherein M represents a mono- or bi-cyclic aromatic ring structure (preferably, phenyl or indolyl, eg 5-indolyl) optionally having at least one (eg,1 or 2 substituents) substituent (eg,1 or 2 substituents) selected from CN; NR12R13; an optionally substituted C1 to C8 alkyl (preferably, C1 to C4 alkyl, and most preferably methyl); optionally substituted C1 to C8 alkoxy (preferably, C1 to C8 alkoxy, and most preferably methoxy); halogen (eg, F, Br or Cl); $CH_2)_b$-C(O)NR12R13 (preferably, $CONH_2$; CH_2CONH_2; or $CH_2CONHCH_3$); NR12-C(O)NR13R14 (preferably, NH-

$C(O)NH_2$); $(CH_2)_b$-$SO_2NR12R13$ (preferably, $CH_2SO_2NHCH_3$); NR12C(O)R13 (eg, $NHC(O)CH_3$; $NR12SO_2R13$; $(CH_2)_bOH$ (preferably, OH or CH_2OH); NR12CN(preferably, NHCN); and $CR12(CN)_2$ (preferably, $CH(CN)_2$).

In one embodiment, option (iv) represents phenyl substituted with two methyl groups (eg, 3,5-dimethylphenyl.

Each R5, R6, R10, R11, R12, R13 and R14 is independently selected from H; optionally substituted C1 to C8 alkyl (preferably, C1 to C4 alkyl, and most preferably methyl) and optionally substituted aryl (eg, optionally substituted phenyl).

R9 is selected from H; optionally substituted C1 to C8 alkyl (preferably, C1 to C4 alkyl, and most preferably methyl); optionally substituted aryl (eg, optionally substituted phenyl); -R-Ar, where R represents C1 to C8 alkylene (preferably, C1 to C4 alkylene, and most preferably methylene) and Ar represents optionally substituted aryl (eg, optionally substituted phenyl); and optionally substituted 3- to 8- membered heterocyclic ring (eg, a 5- or 6-membered ring) optionally containing from 1 to 3 further heteroatoms (eg, 1 further heteroatom) independently selected from O, N and S.

X represents O; S; or NR''', where R''' is H or C1 to C8 alkyl (preferably, C1 to C4 alkyl, and most preferably methyl).

Y represents a bond; C1 to C8 alkylene (preferably, C1 to C4 alkylene, and most preferably methylene); a C2 to C12 group having at least one alkene double bond; or a C2 to C12 group having at least one alkyne triple bond. Where Y represents a C2 to C12 group having at least one alkene double bond, this may have from 1 to 11 (more preferably 1 to 8) alkene double bonds (eg, 1, 2 or 3 alkene double bonds). The group can be straight chain or branched. Where Y represents a C2 to C12 group having at least one alkyne triple

bond, this may have from 1 to 6 alkyne triple bonds (eg, 1, 2 or 3 alkyne triple bonds). The group can be straight chain or branched.

Z represents a bond; C1 to C8 alkylene (preferably, C1 to C4 alkylene, and most preferably methylene); a C2 to C12 group having at least one alkene double bond; a C2 to C12 group having at least one alkyne triple bond; or -CR(R'), where R and R' are independently selected from H, CN, halogen (eg, F, Br or Cl, most preferably F), C1 to C8 alkyl (preferably, C1 to C4 alkyl, and most preferably methyl), CH_2F, CHF_2, and C3 to C8 cycloalkyl (preferably, C3 to C6 cycloalkyl). Where Z represents a C2 to C12 group having at least one alkene double bond, this may have from 1 to 11 (more preferably 1 to 8) alkene double bonds (eg, 1, 2 or 3 alkene double bonds). The group can be straight chain or branched. Where Z represents a C2 to C12 group having at least one alkyne triple bond, this may have from 1 to 6 alkyne triple bonds (eg, 1, 2 or 3 alkyne triple bonds). The group can be straight chain or branched.

Z' represents a bond; C1 to C8 alkylene (preferably, C1 to C4 alkylene, and most preferably methylene); a C2 to C12 group having at least one alkene double bond; a C2 to C12 group having at least one alkyne triple bond; or -CR(R'), where R and R' are independently selected from H, CN, halogen (eg, F, Br or Cl, most preferably F), C1 to C8 alkyl (preferably, C1 to C4 alkyl, and most preferably methyl), CH_2F, CHF_2, and C3 to C8 cycloalkyl (preferably, C3 to C6 cycloalkyl). Where Z' represents a C2 to C12 group having at least one alkene double bond, this may have from 1 to 11 (more preferably 1 to 8) alkene double bonds (eg, 1, 2 or 3 alkene double bonds). The group can be straight chain or branched. Where Z' represents a C2 to C12 group having at least one alkyne triple bond, this may have from 1 to 6 alkyne triple bonds (eg, 1, 2 or 3 alkyne triple bonds). The group can be straight chain or branched.

For the integers a and b,

a = zero or an integer from 1 to 8 (preferably, a = zero); and

each b is independently selected from zero or an integer from 1 to 8 (preferably, each b = zero). In one embodiment, a represents zero and Y represents CH_2.

The ring **B** can be optionally further substituted.

In the present specification, unless otherwise indicated, an alkyl, alkylene or alkenyl moiety (eg, the alkyl moiety of an alkylaryl substituent) may be linear or branched.

The term "alkylene" refers to $-CH_2-$. Thus, C8 alkylene for example is $-(CH_2)_8-$.

Where optional substitution is mentioned at various places above, this refers to one, two, three or more optional substituents. Unless otherwise indicated above (ie, where a list of optional substituents is provided), each substituent can be independently selected from C1 to C8 alkyl (preferably C2 to C6 alkyl, and most preferably methyl); O(C3 to C8 cycloalkyl), preferably O-cyclopropyl, or O-cyclobutyl or O-cyclopentyl; O(C1 to C6 alkyl), preferably Omethyl or O(C2 to C4 alkyl); halo, preferably Cl or F; $CHal_3$, $CHHal_2$, CH_2Hal, $OCHal_3$, $OCHHal_2$ or OCH_2Hal, wherein Hal represents halogen (preferably F); CH_2OR, NRCOR′, $NRSO_2R'$ or N-R-R′, wherein R and R′ independently represent H or C1 to C8 alkyl (preferably methyl or C2 to C6 alkyl or C2 to C4 alkyl) , or N-R-R′ represents an optionally substituted C3 to C8, preferably C3 to C6, heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; H; or COOR″ or COR″, R″ representing H, optionally substituted phenyl or C1 to C6 alkyl (preferably methyl, ethyl, *i*-propyl or *t*-butyl). For optional substitution of the heterocyclic ring represented by N-R-R′, at least one (eg, one, two or three) substituents may be provided independently selected from C1 to C6 alkyl (preferably C2 to C4 alkyl, more preferably methyl); phenyl; OCF_3; $OCHF_2$; -O(C1-C8 alkyl), preferably –O-methyl, -O-ethyl or –O(C3 to C6 alkyl); -C(O)O(C1-C8 alkyl), preferably –C(O)O-methyl, -C(O)O-ethyl, -C(O)O-*tert*-butyl or –C(O)O(C3 to C6 alkyl); -C(O)O-phenyl; -O-phenyl; -C(O) (C1-C8 alkyl), preferably –C(O)-methyl, -C(O)-ethyl or –C(O)(C3 to C6 alkyl) ; -C(O)OH; -S(C1-C8 alkyl), preferably –S-methyl, -S-ethyl or –S(C3 to C6 alkyl); OH; halogen (eg, F, Cl or Br), NRR' where R and R' are independently H or C1 to C6 alkyl

(preferably C2 to C4 alkyl, more preferably methyl, most preferably R=R'=methyl); and nitro.

Particularly preferred compounds according to the present invention are:-

N-Benzyl-*N*-methyl-2-(4-bromophenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(4-chlorophenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(4-fluorophenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(4-cyanophenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(4-methoxyphenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(3,4-dimethoxyphenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(3,4-dichlorophenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(4-bromophenyl)-5-diethylamido-3-methylamino-imidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(4-bromophenyl)-5-isopropyloxycarbonyl-3-methylamino-imidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(4-isopropylamidophenyl)-5-isopropyloxycarbonyl-3-methylamino-imidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(3,4,5-trimethylphenyl)-5-diethylamido-3-methylamino-imidazo[1,2-*a*]pyridine;

Ethyl *N*-benzyl-*N*-methyl-5-(3-acetamidophenyl)-3-methylamino-imidazo[1,2-*a*]pyridine-2-carboxylate;

N-Cyano-*N*'-[3-(1H-indol-5-yl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N*''-methyl-guanidine;

N-Cyano-*N*'-[3-(3,4-dimethoxyphenyl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N*''-methyl-guanidine;

N-Cyano-*N*'-[3-(4-chlorophenyl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N*''-methyl-guanidine;

N-Cyano-*N*'-[3-(3,5-dimethylphenyl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N*''-methyl-guanidine;

N,*N*-Dibenzyl-2-methylamino-3-(3,4-dimethoxyphenyl)imidazo[1,2-*a*]pyridine;

N,*N*-Dibenzyl-2-methylamino-3-(4-dimethoxyphenyl)imidazo[1,2-*a*]pyridine;

N-benzyl-*N*-methyl-2-methylamino-3-(4-chlorophenyl)imidazo[1,2-*a*]pyridine;

N-benzyl-*N*-methyl-2-methylamino-3-(3,5-dimethylphenyl)imidazo[1,2-*a*]pyridine;

N-Benzyl-5-bromo-3-(3-methylpropylamino)-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-Methyl-5-methyl-3-propargylamino-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine;

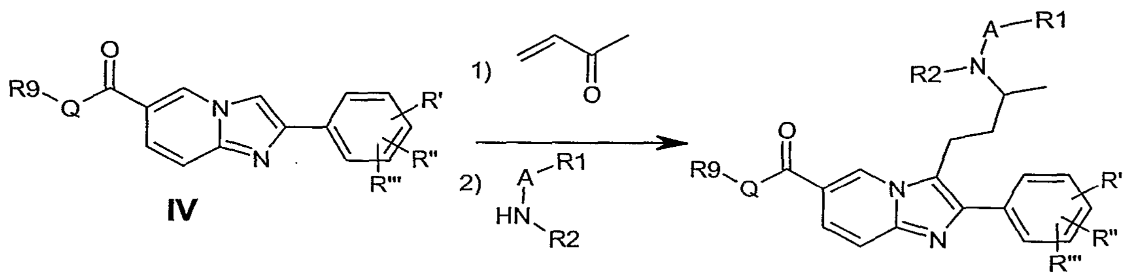
N-(β-methylphenethyl)-*N*-Methyl-5-methyl-3-propargylamino-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine; and

N-Benzyl-*N*-methyl-2-(3,5-dimethylphenyl)-3-ethylamino-5-methylimidazo[1,2-*a*]pyridine.

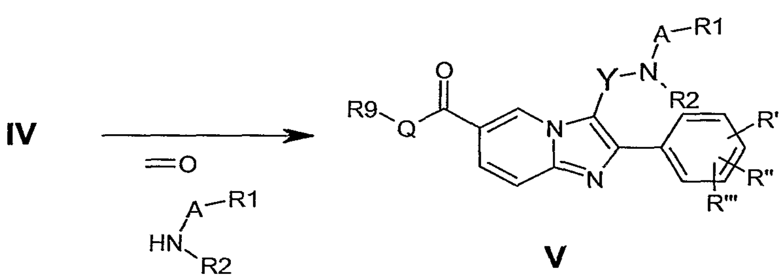
The invention also contemplates pharmaceutically acceptable salts and solvates of these compounds. Compounds of formula **I** may be converted to pharmaceutically acceptable salts and solvates thereof, preferably acid addition salts, such as hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartarate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or alkali metal salts such as sodium or potassium salts.

The compounds of formula **I** can be prepared by a process comprising a step selected from (a) to (y) as follows:-

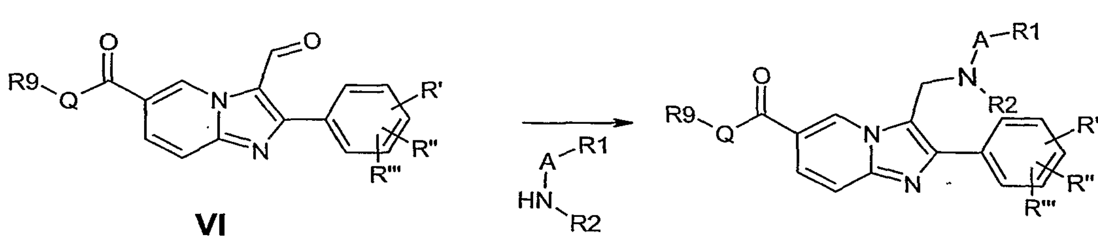
(a) Reaction of a compound of formula **IV** as follows



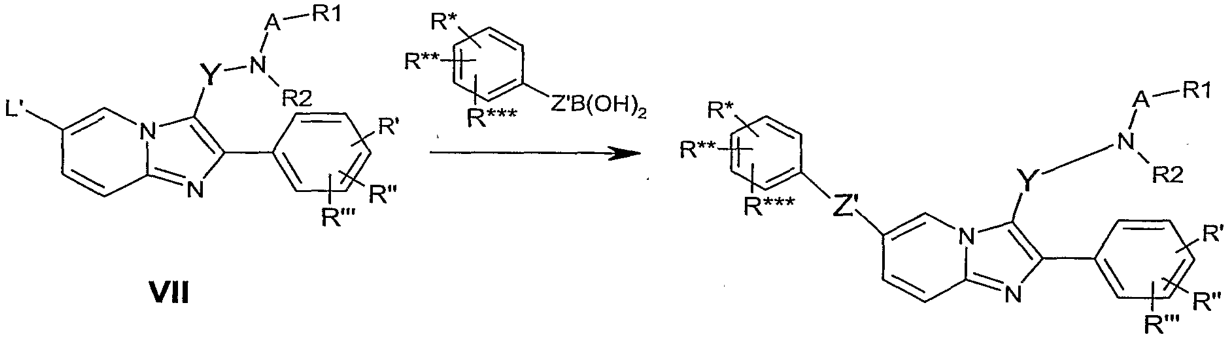
(b) Reaction of a compound of formula **IV** as follows



(c) Reaction of a compound of formula **VI** as follows

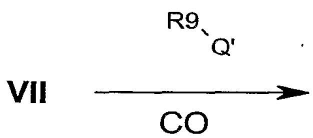


(d) Reaction of a compound of formula **VII** as follows

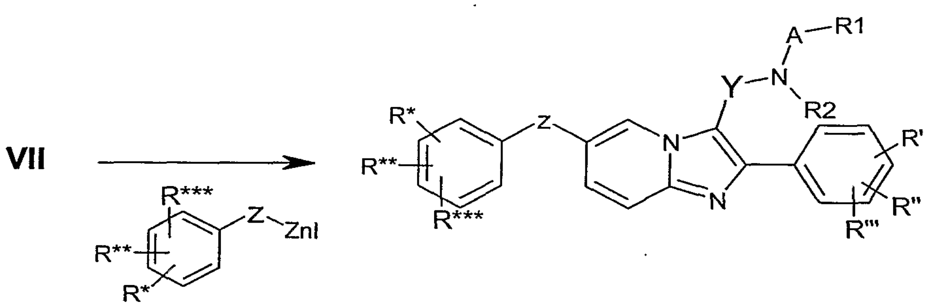


VII

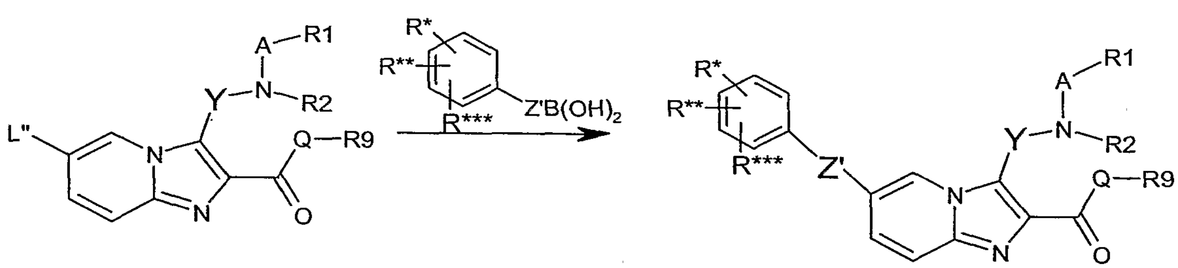
(e) Reaction of a compound of formula **VII** as follows



(f) Reaction of a compound of formula **VII** as follows

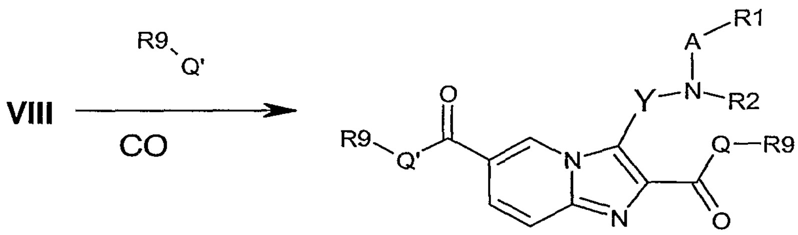


(g) Reaction of a compound of formula **VIII** as follows

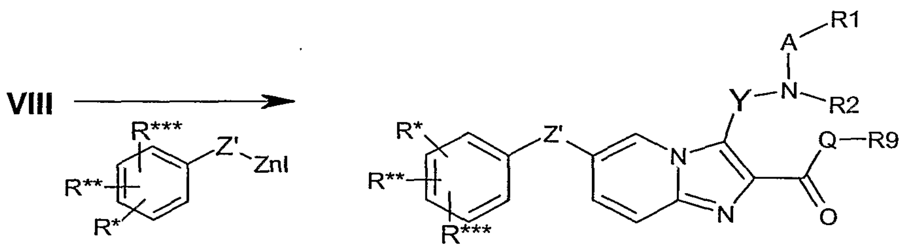


VIII

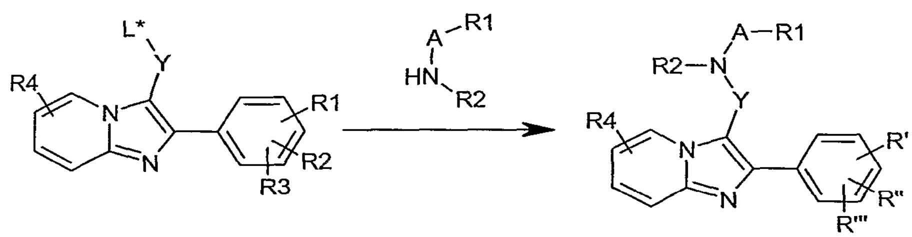
(h) Reaction of a compound of formula **VIII** as follows



(i) Reaction of a compound of formula **VIII** as follows



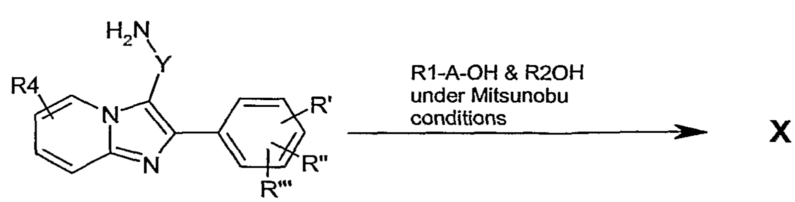
(j) Reaction of a compound of formula **IX** as follows



IX

X

(k) Reaction of a compound of formula **XI** as follows



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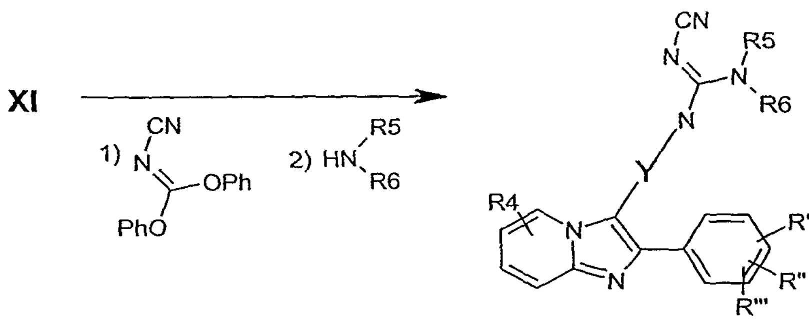
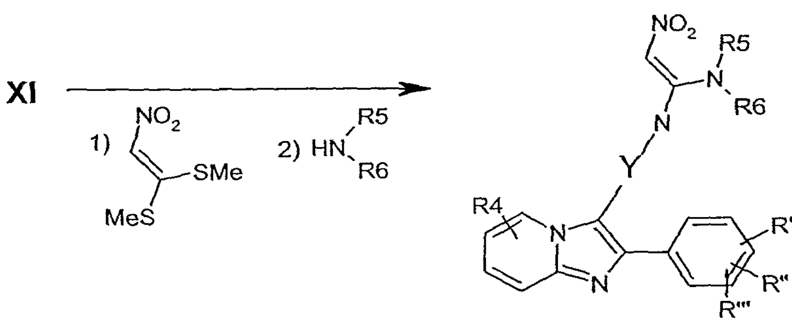
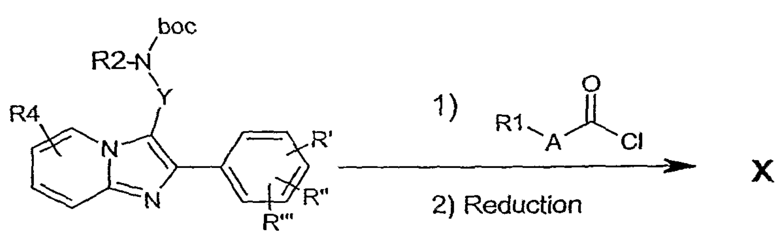
(l) Reaction of a compound of formula **XI** as follows



(m) Reaction of a compound of formula **XI** as follows

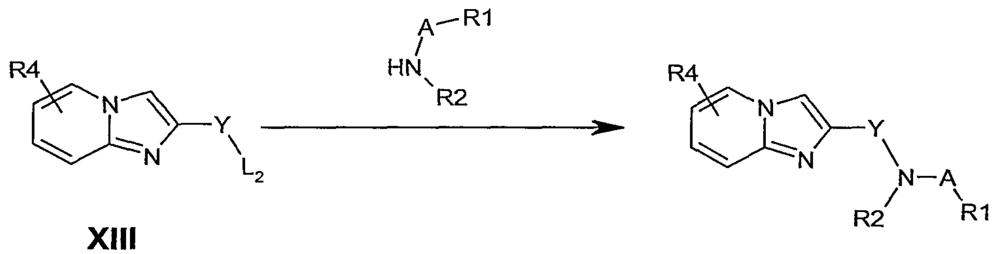


(n) Reaction of a compound of formula **XII** as follows



XII

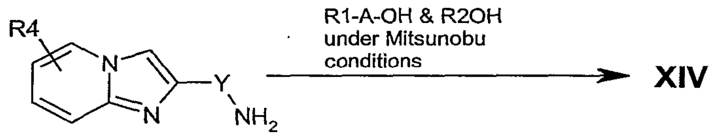
(o) Reaction of a compound of formula **XIII** as follows



XIII

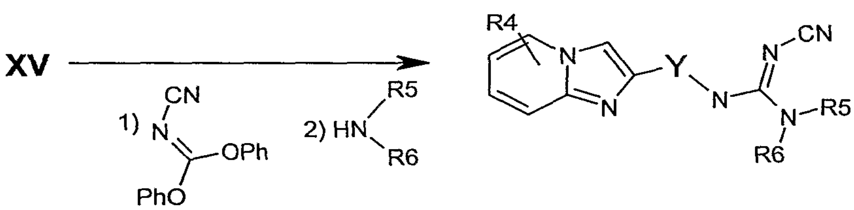
XIV

(p) Reaction of a compound of formula **XV** as follows

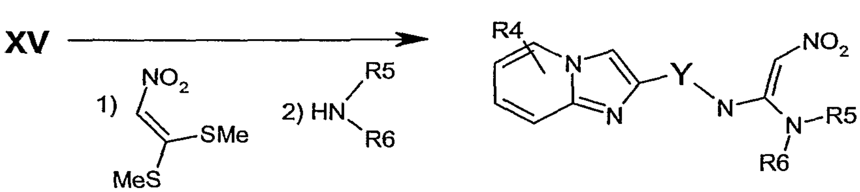


XV

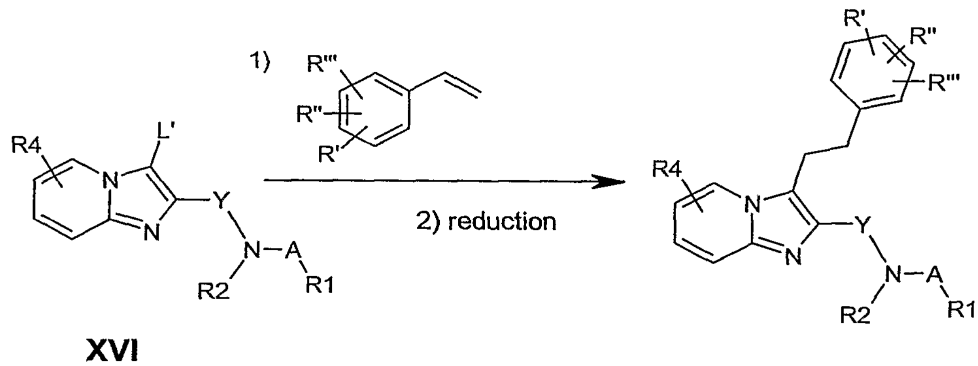
(q) Reaction of a compound of formula **XV** as follows



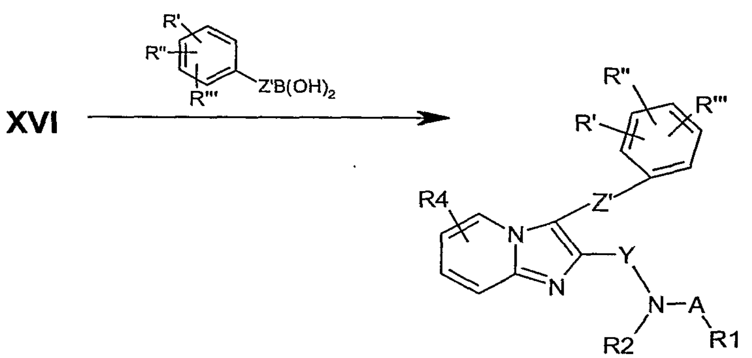
(r) Reaction of a compound of formula **XV** as follows



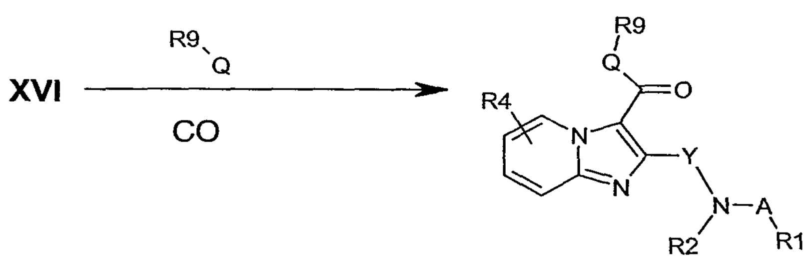
(s) Reaction of a compound of formula **XVI** as follows



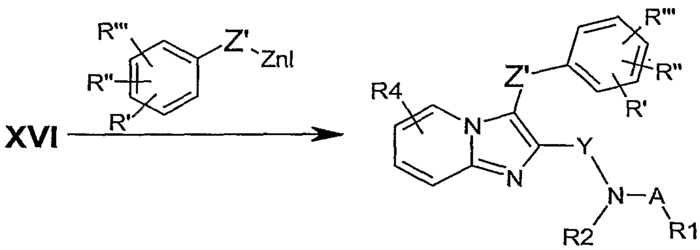
(t) Reaction of a compound of formula **XVI** as follows



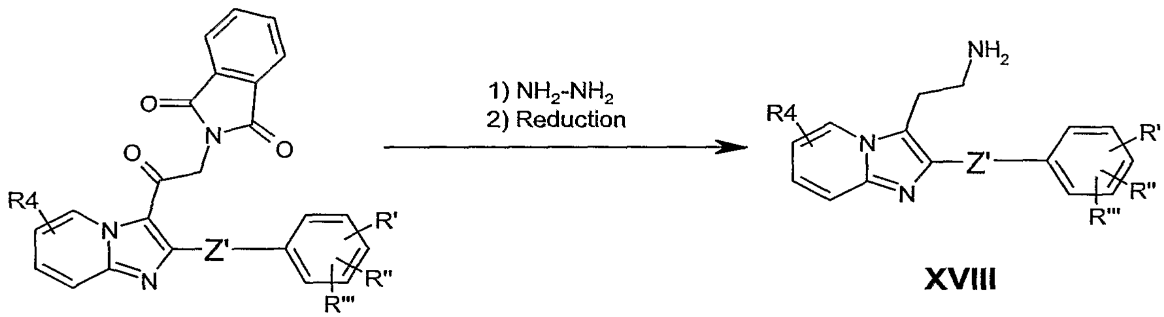
(u) Reaction of a compound of formula **XVI** as follows



(v) Reaction of a compound of formula **XVI** as follows

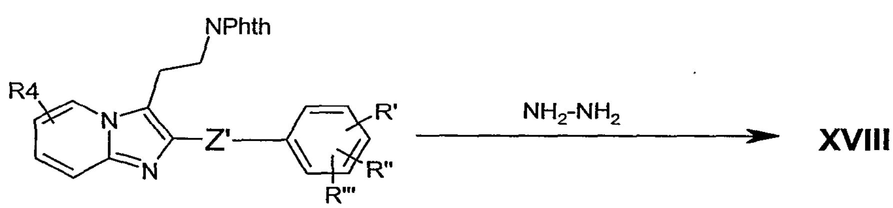


(w) Reaction of a compound of formula **XVII** as follows



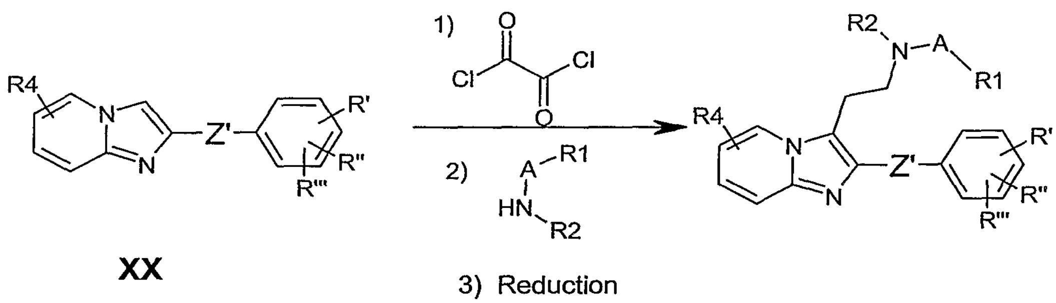
XVII **XVIII**

(x) Reaction of a compound of formula **XIX** as follows



XIX

(y) Reaction of a compound of formula **XX** as follows



XX

Wherein R', R", R"', R*, R** and R*** are independently H or a substituent;

L', L'', L_2 and L* are leaving groups;

Q = NR10; S or O; and

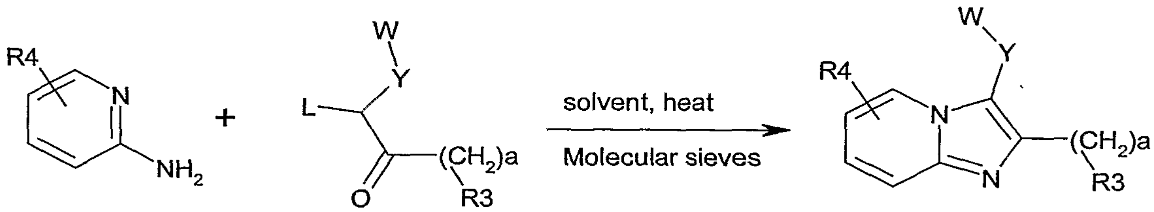
Q' = NR10; S or O.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula **I** may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

EXPERIMENTAL

GENERAL REACTION SCHEMES



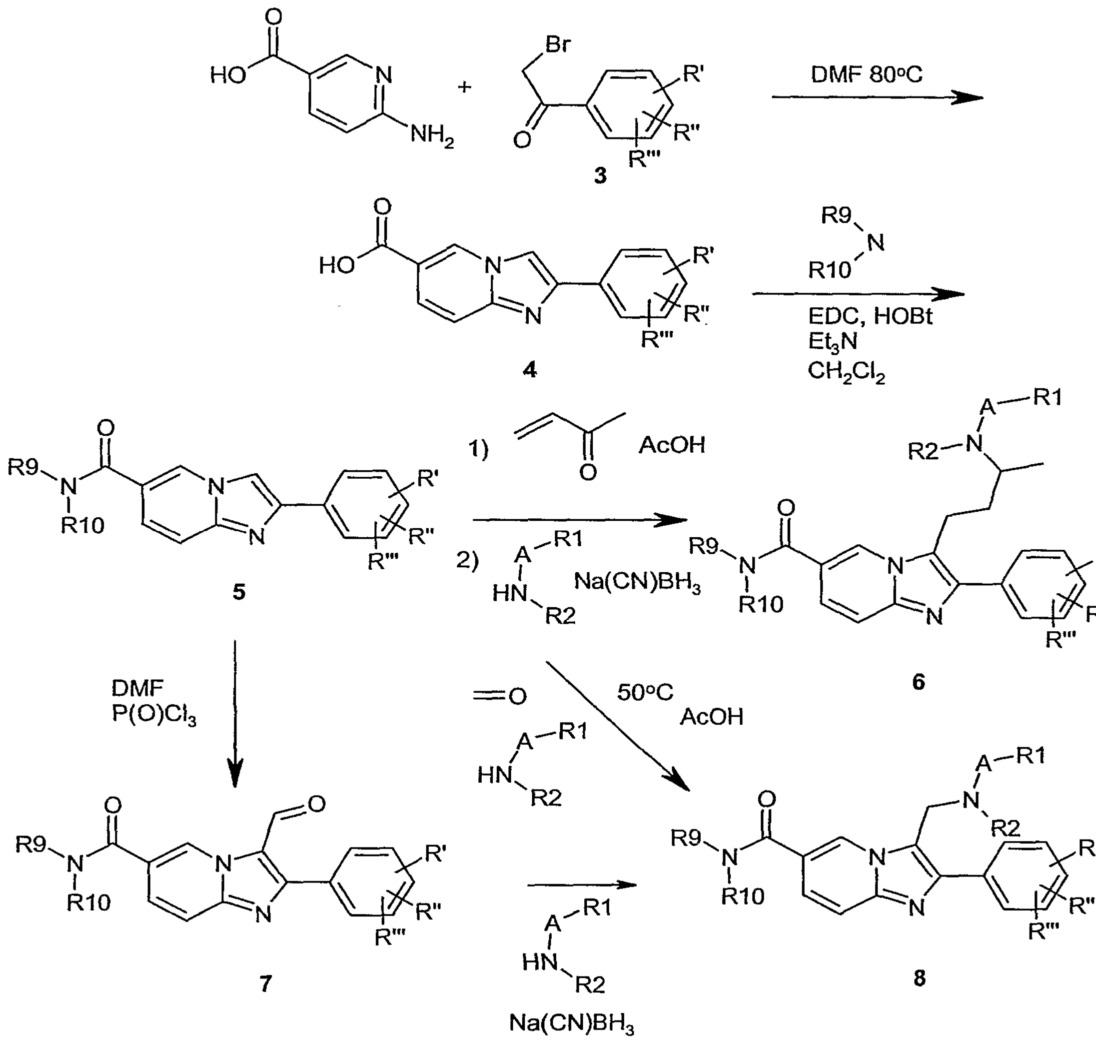
1 2 (A)

Scheme a

L=leaving group e.g. Cl, Br, I, OMesyl, OTosyl or H, W = epoxide or aziridines

W=group for elaboration into N(-(A)-R1)R2.

Imidazo[1,2-*a*]pyridines of the structure **(A)** can be prepared by the condensation of a suitable substituted 2-aminopyridine **1** and a ketone **2** bearing a leaving group α to the carbonyl group (Br preferred group). Heating at a temperature between 25 °C and 120 °C, preferably 80 °C, in a suitable solvent such as *N.N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO), toluene, xylene, *t*-BuOH, preferable DMF, with or without the molecular sieves, for a period of 1 to 24 h, effects the condensation. With appropriately substituted groups (e.g. W), the amine group -N(-(A)-R1)R2 can then be installed by standard chemistry know to those skilled in the art which is detailed below.

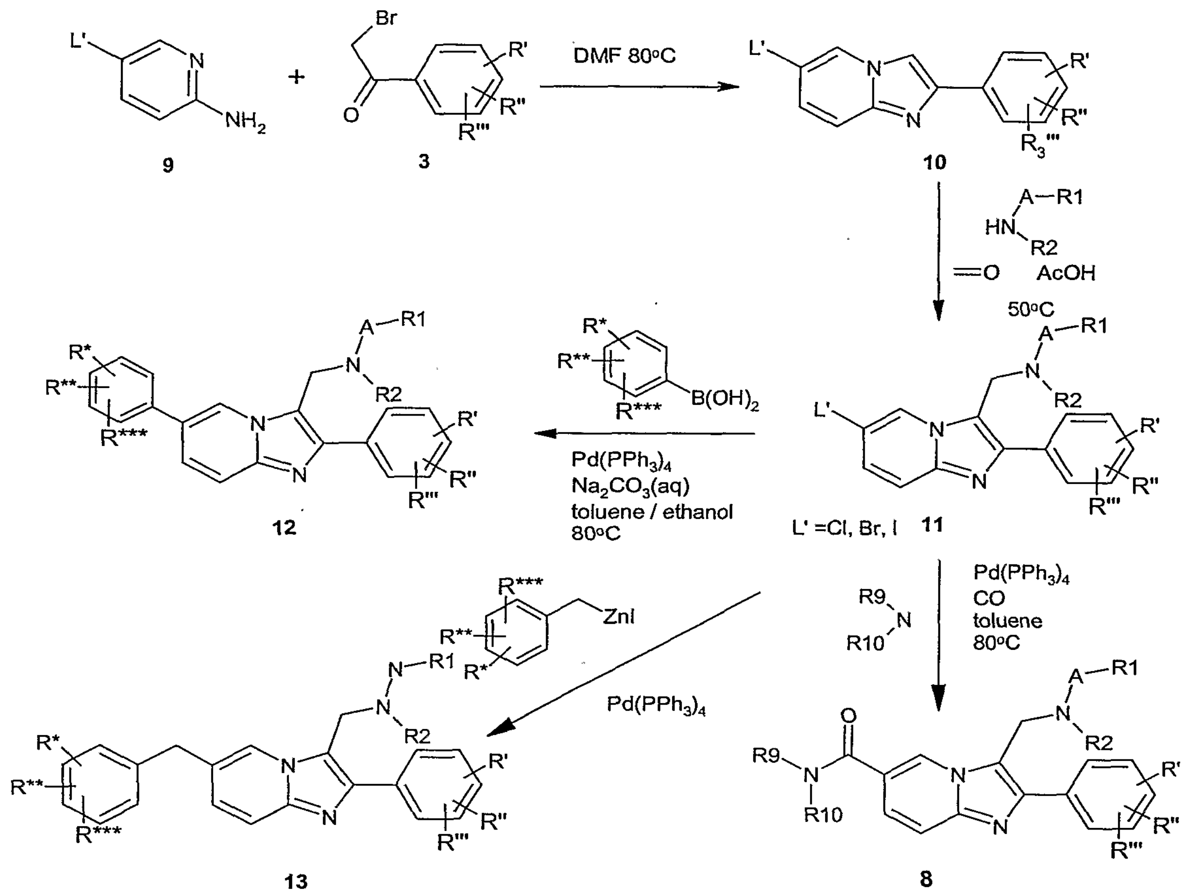


Scheme b

For example, Scheme b shows a general synthesis of 5-carbonyl-2-aryl-3-aminomethylimidazo[1,2-*a*]pyridine commencing with commercially available 2-aminopyridine and 2'-bromoacetophenone. Thus, condensation of 6-aminonicotinic acid and a 2'-bromoacetophenone **3,** under the preferred conditions noted above for the key cyclisation, yields the bicycle **4.** Condensation using the coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1,3-dicyclohexylcarbodiimide (DCC) or the like, with or without 1-hydroxybenotriazole (HOBt) and suitable amine base, such as triethylamine and the like, in an inert solvent such as methylene chloride, chloroform, DMF, or mixtures thereof, at or near room temperature

for a period of 3 to 24h to provide the corresponding coupled product **5,** bearing the substituent N(R9)R10, where R9 and R10 are as defined above. Michael addition reactions can be achieved by the condensation of methyl vinyl ketone with the bicycle **5** by heating in an organic acid, such as acetic acid, to yield a ketone product. Reductive amination under typical conditions of an appropriately substituted amine and a hydride source, such as sodium cyanoborohydride, sodium borohyride, zinc borohyride, lithium borohydride and the like, yields products such as **6**. Using classical Mannich chemistry an aminomethyl group can be introduced by treatment of **5** with a mixture of a suitably substituted amine (NH(A-R1)(R2)) and paraformaldehyde. In an organic acid such as acetic acid and the like and stirring at room temperature or heating between 40 and 100°C in this manner compounds such as **8** which correspond to the general structure **(A)** where Y represents CH_2 are formed. Alternatively, a two step procedure may be employed, where a Vilsmeier reaction, classically employing DMF and phosphorus oxychloride at a temperature between -10 °C and 25 °C, installs a formyl group at the 3-position of the imidazo[1,2-a]pyridine to give **7**. Reduction amination employing a suitably substituted amine [HN(-(A)-R1)R2] and a reducing agent such as sodium borohydride, sodium cyanoborohydride, zinc borohydride and the such like, under acid or neutral conditions in a suitable solvent such as methylene chloride, chloroform, benzene, toluene and alcohols such as ethanol and the like, yields the 3-aminomethyl-imidazo[1,2-a]pyridines **(8)**.

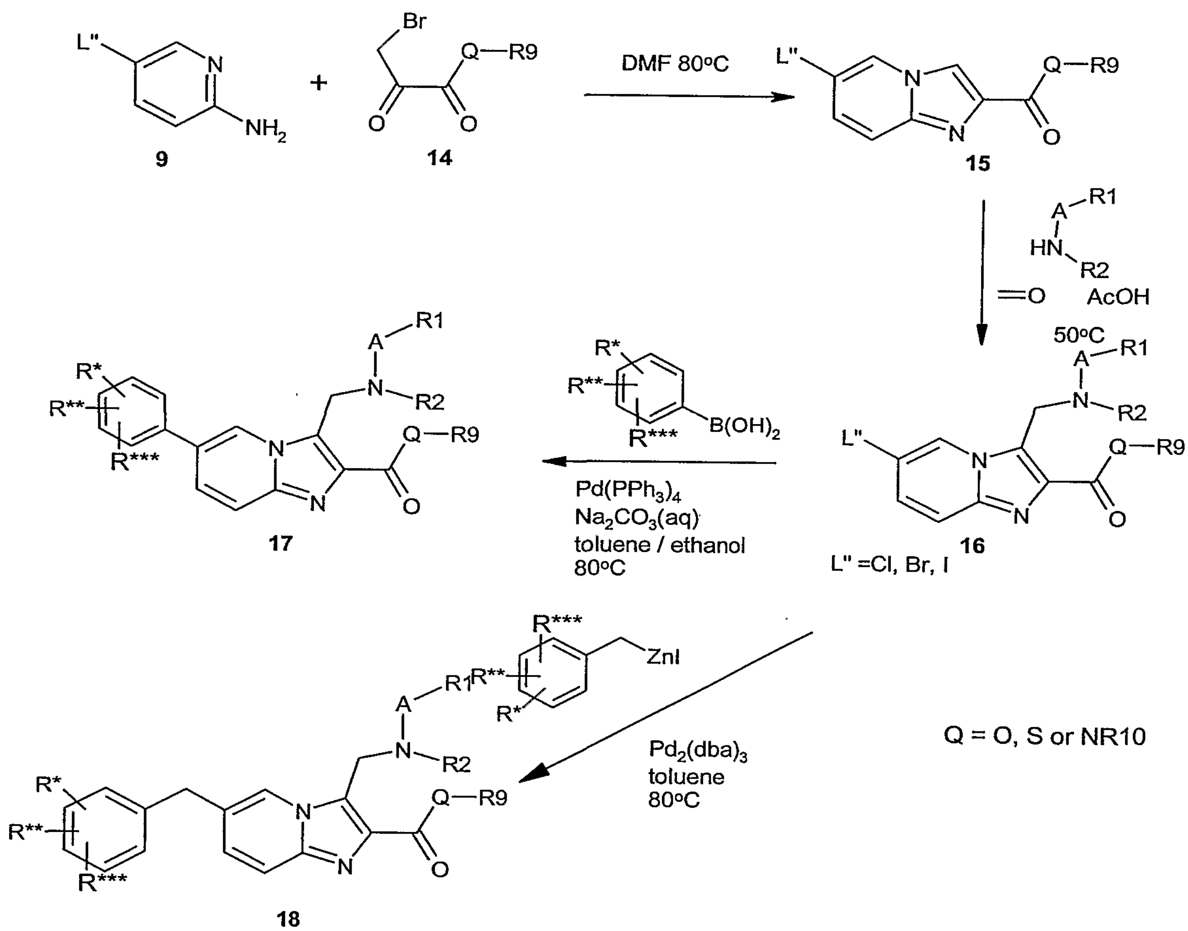
As an alternative to N(R9)R10, one can use R9OH in scheme b.



Scheme c

For example, Scheme c shows another general synthesis of 5-carbonyl-2-aryl-3-aminomethylimidazo[1,2-*a*]pyridine commencing with commercially available 2-aminopyridines and 2'-bromoacetophenone. Thus, condensation of 2-aminopyridine **9** and a 2'-bromoacetophenone **3** under the preferred conditions noted above for the key cyclisation yields the bicycle **10**. The Mannich reaction conditions described above for Scheme b again install the substituted aminomethyl group leading to the bicycle **11**. Where L' is chloride, bromide, iodide, O-trifluoromethanesulfonate, trialkyltin or like, **11** can be treated under palladium(0) catalysis with carbon monoxide at 1atm or higher pressure in the presence of a substituted amine (N(R9) R10 as shown), alcohol (R9OH – not shown) or thiol (R9SH – not shown) in an inert solvent such as toluene, benzene, dioxane, THF, DMF and the like to yield 5-carbonyl-2-aryl-3-aminomethylimidazo[1,2-*a*]pyridines such as **8**. Where L' is chloride, bromide, iodide, O-trifluoromethanesulfonate, trialkyltin or like **11** can be treated under palladium(0), a weak base such aqueous sodium carbonate and the

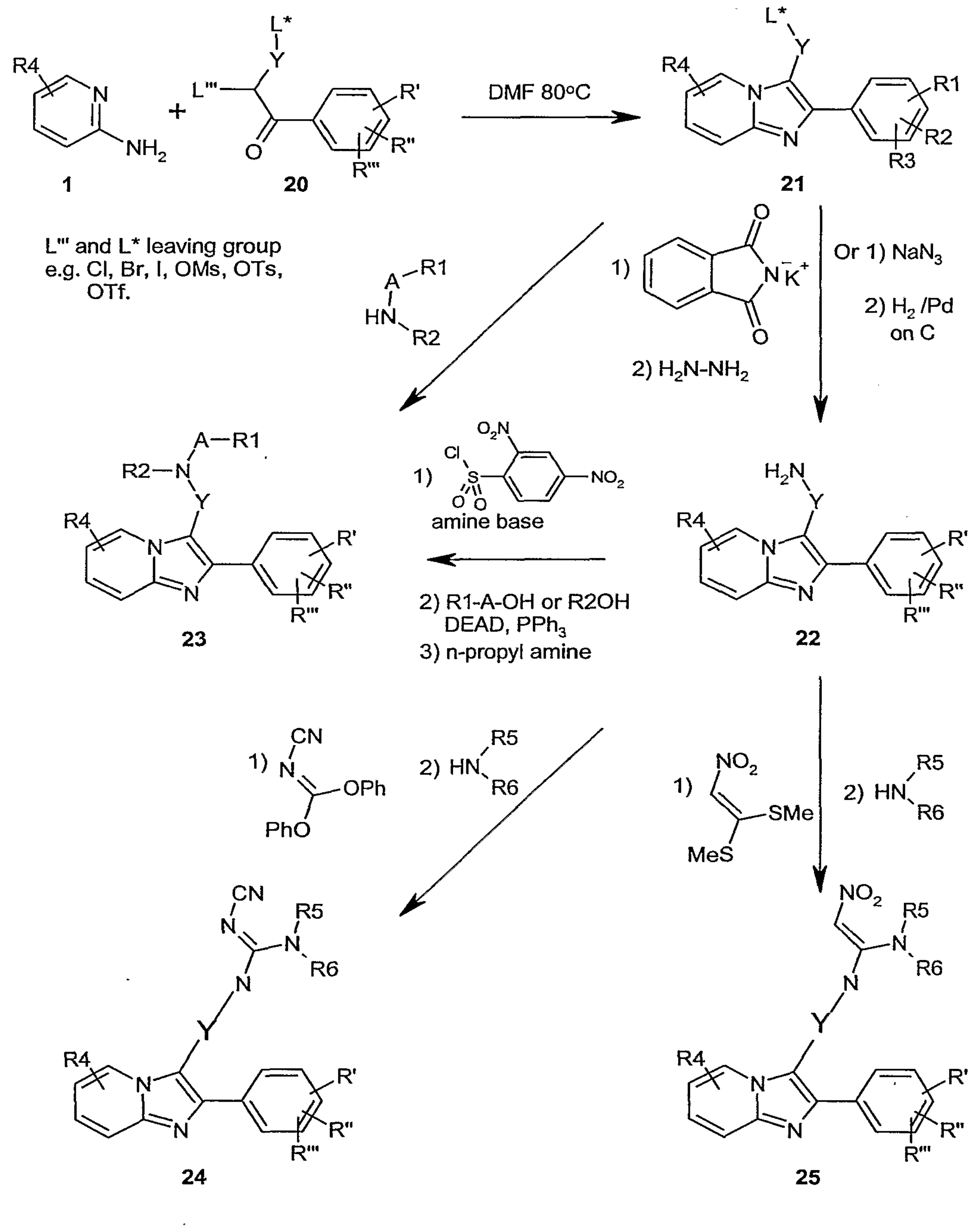
like and a substituted aryl boronic acid from commercial sources or prepared (as described in: Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y.,-H *Chem. Sci.* **1986**, *26*, 311-314), in an inert solvent such as toluene, benzene, dioxane, THF, DMF and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours, to give the imidazo[1,2-*a*]pyridine **12**. Similarly coupling of an arylalkylzinc iodide with **11** can be achieved using the methods of Negishi (e.g. Jackson, R. F. W.; James, H.; Wythes, M. J.; Wood, A. *J. Chem. Soc. Chem. Commun.* **1989**, 644) to yield imidazo[1,2-*a*]pyridines (**13**).



Scheme d

Condensation of a suitable substituted 2-aminopyridine **9** with a bromopyruvate **14** using the condition described above, yields 2-carboxyimidazo[1,2-*a*]pyridines **15**. With same chemical sequences of Mannich reaction then palladium catalysed carbonylation, Suzuki couplings or Negishi couplings the 2-carboxyimidazo[1,2-*a*]pyrimidines **17** and **18** can be synthesised (Scheme d).

As an alternative to N(R9)R10, one can use R9OH in scheme d.

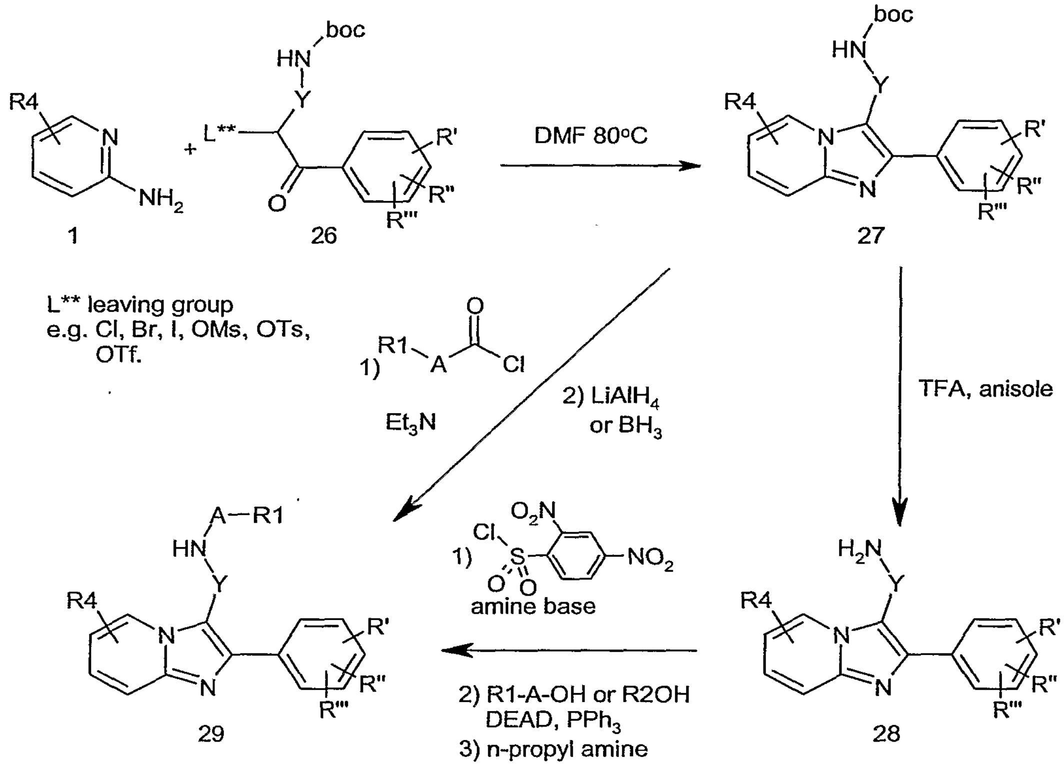


Scheme e.

Condensation of a suitable 2-aminopyridine **1** and a substituted aryl ketone **20**using the conditions described above gives imidazo[1,2-*a*]pyridines of the type **21** where a 3-position is already substituted with an alkyl chain. The leaving group L* can be converted

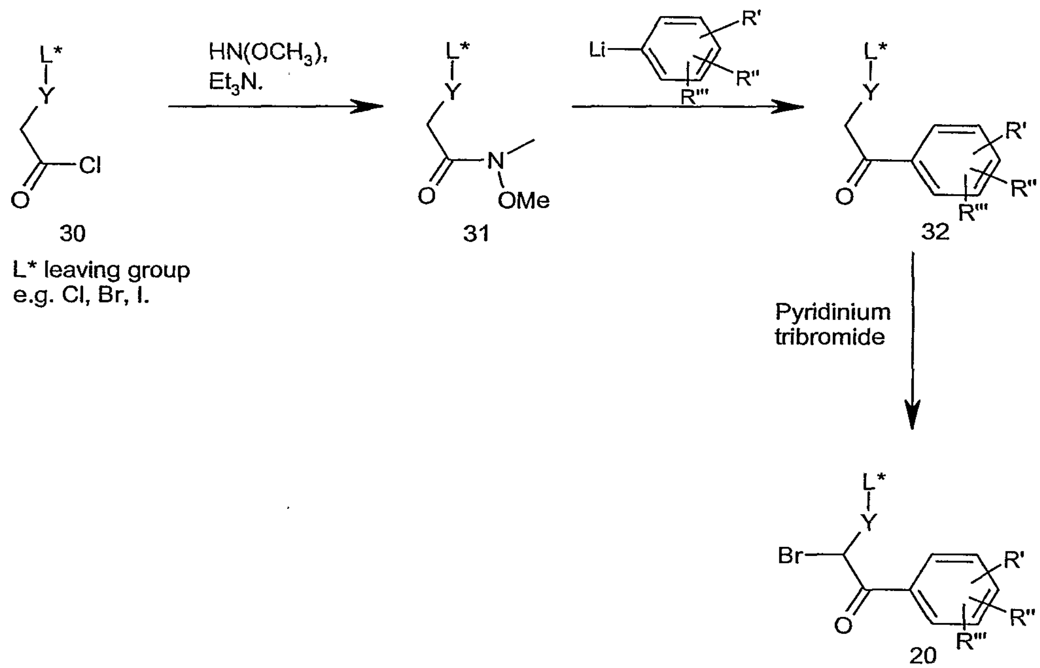
to an amine (**22**) by either the two step route of :- displacement with potassium phthalimide (heating in a suitable inert solvent such as DMSO, DMF or THF and mixtures thereof, and the like) then removal of the phthalimide protecting group (treatment with hydrazine in an inert solvent e.g. methylene chloride, chloroform, THF and mixtures thereof and the like), or displacement with sodium azide (heating in a suitable solvent DMSO, DMF or THF and mixtures thereof and the like) then reduction of the resultant azide (by treatment with hydrogen gas at atmospheric pressure or under high pressure [up to 600 psi] under palladium catalysis, or by Stoedinger reduction with triphenylphosphine). Groups R1 and R2 can be introduced by a modified Mitsunobu reaction. Reaction with an arylsufonyl chloride such as 2-nitrobenzenesulphonyl chloride, 4-nitrobenzenesulphonyl chloride, 2,4-nitrobenzenesulphonyl chloride and a hindered amine base such as 2,4,6-collidine, 2,6-lutidine or the like in an inert organic solvent such as methylene chloride, provides the corresponding sulfonamide. Mitsunobu coupling of the sulfonamide and an alcohol (R1OH or R2OH) can be achieved by treatment with an activating agent such as diethyldiazocarboxylate (DEAD), diisopropyldiazocarboxlate or the like with triphenylphosphine, tri-butylphosphine and the like, in an inert solvent such as benzene, toluene, tetrahydrofuran or mixtures thereof to give the dialkylated sulfonamide adduct. Removal of the sulfonamide group is accomplished by treatment with a nucleophilic amine such as *n*-propylamine to give substituted amine **23.**

The primary amine **22** can be converted to a cyano-guanidine (**24**) by the two step process of reaction with diphenyl cyanocarbonimidate in an inert organic solvent such as methylene chloride, chloroform, benzene, tetrahydrofuran and the like, followed by condensation with an appropriately substituted amine (HNR5R6) in an inert organic from the list above. Similarly, reaction with 1,1'-bis(methylthio)-2-nitroethylene in an inert solvent such methylene chloride, chloroform, benzene, tetrahydrofuran and the like, followed by condensation with an appropriately substituted amine (HNR5R6) in an inert organic solvent from the list above yields the nitroethyleneimidazo[1,2-*a*]pyridine **25**.



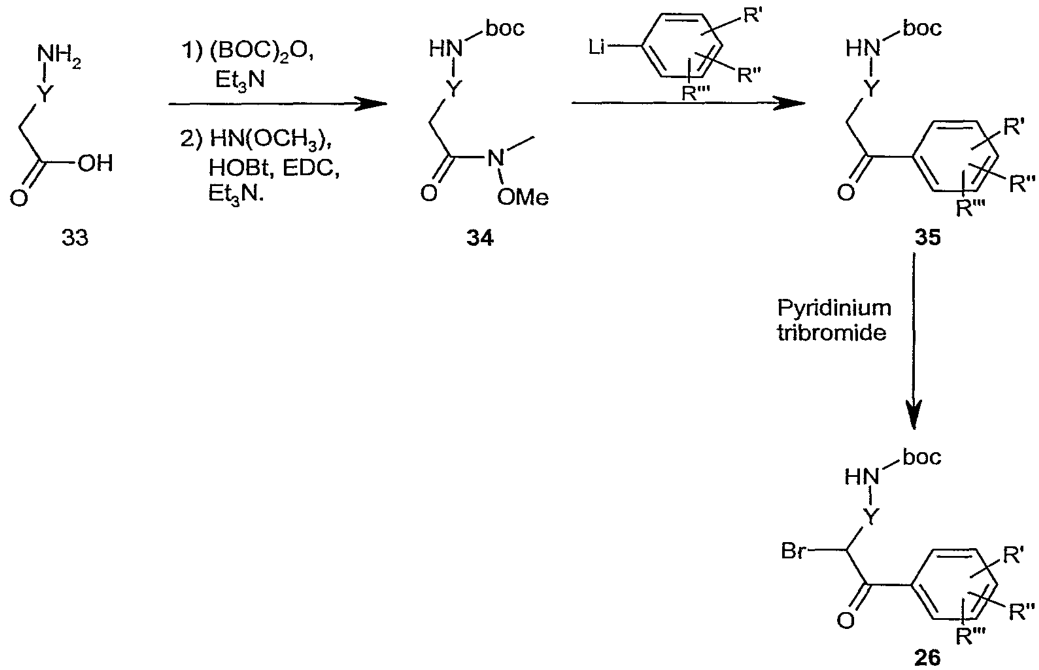
Scheme f

Condensation of 2-aminopyridines **1** with ketones bearing a *t*-butylcarbamate protected nitrogen atom **(26)** produces imidazo[1,2-*a*]pyridines such as **27**, where the nitrogen atom is already installed (Scheme f). The *t*-butylcarbamate protecting group is removed by treatment with an organic acid such as trifluoroacetic acid and the like, in the presence of a carbocation scavenger such as anisole, to yield the same imidazo[1,2-*a*]pyridines **28** as in scheme f. In the same manner the substitutents on the nitrogen atom can be installed by the Mitsunobu strategy **(28→29)** or by condensation with an acid chloride in the presence of a hindered amine base such as triethylamine, in an inert solvent such as methylene chloride, then reduction of this product with lithium aluminium hydride, in an inert solvent such as tetrahydrofuran, or by reduction with borane in a similarly inert solvent **(27→29)**.



Scheme g.

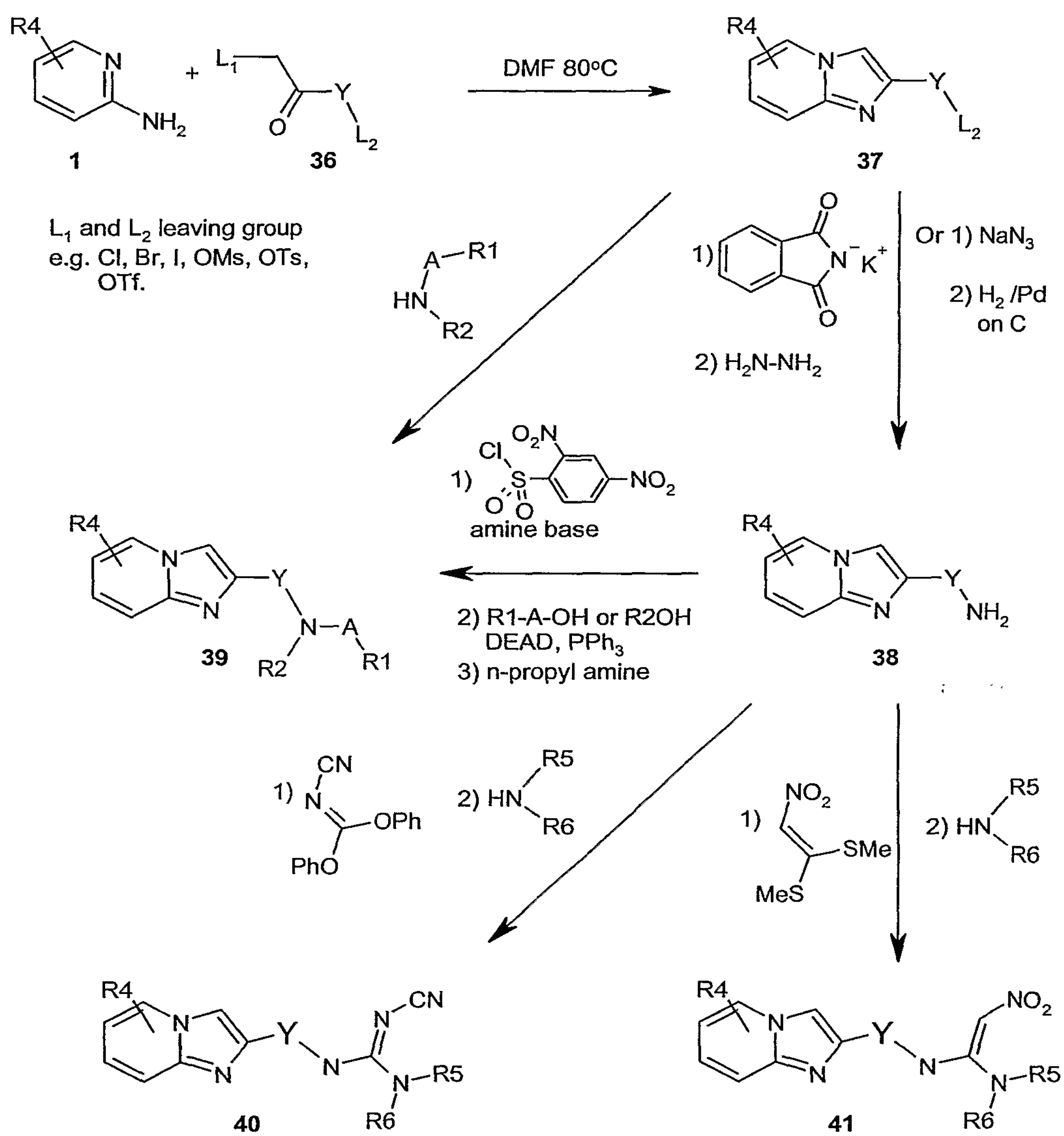
Substituted ketones (**20**) can be prepared, as outlined in Scheme g starting from appropriate acid chlorides such as **30**. Treatment of the acid chloride with *N,N*-dimethylhydroxylamine in the presence of an amine base such as triethylamine, and a suitable solvent such as methylene chloride at a temperature of -10 °C to 25 °C, yields the amide **31**. Further reaction with a substituted aryl organolithium (prepared essentially as described in Wakefield B, J.; *Organolithium Methods* Academic Press Limited, **1988**, pp. 27-29 and references therein) in an inert solvent such as tetrahydrofuran, diethyl ether, benzene, toluene or mixture thereof and the like, at a temperature between -100 °C and O °C then quenching of the reaction mixture with a mineral acid such as hydrochloric acid, yields the aryl ketone **32**. Finally treatment of **32** with a bromine source such as pyridinium tribromide or pyrrolidone hydrobromide in an inert solvent such as chloroform or methylene chloride at -10 °C to 25 °C, yields a bromoketone **20** which is appropriate for the formation of an imidazo[1,2-*a*]pyridine.



Scheme h.

Commencing with a readily available amino acid with a suitable chain length for Y (**33**), the nitrogen atom can be installed directly by the route shown in Scheme h. Protection of the amine group of **33** with a *tert*-butylcarbamate group is achieved by condensation with di-*tert*-butyl dicarbonate in the presence of an amine base, for example triethylamine, in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran and mixtures thereof and the like, at a temperature of -10 °C to 25 °C. Coupling of the acid product with *N,N*-dimethylhydroxylamine in the presence of a coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1,3-dicyclohexylcarbodiimide (DCC) or the like, with or without 1-hydroxybenotriazole (HOBt), and suitable amine base, such as triethylamine and the like, in an inert solvent such as methylene chloride, chloroform, dimethylformamide, or mixture thereof, at or near room temperature for a period of 3 to 24 h provided the corresponding coupled product **34**. Following the same route described above for scheme g, the aryl group can then be

installed and subsequently the α-bromo group to give the ketone **26**, which is suitable for condensation with a 2-aminopyridine.

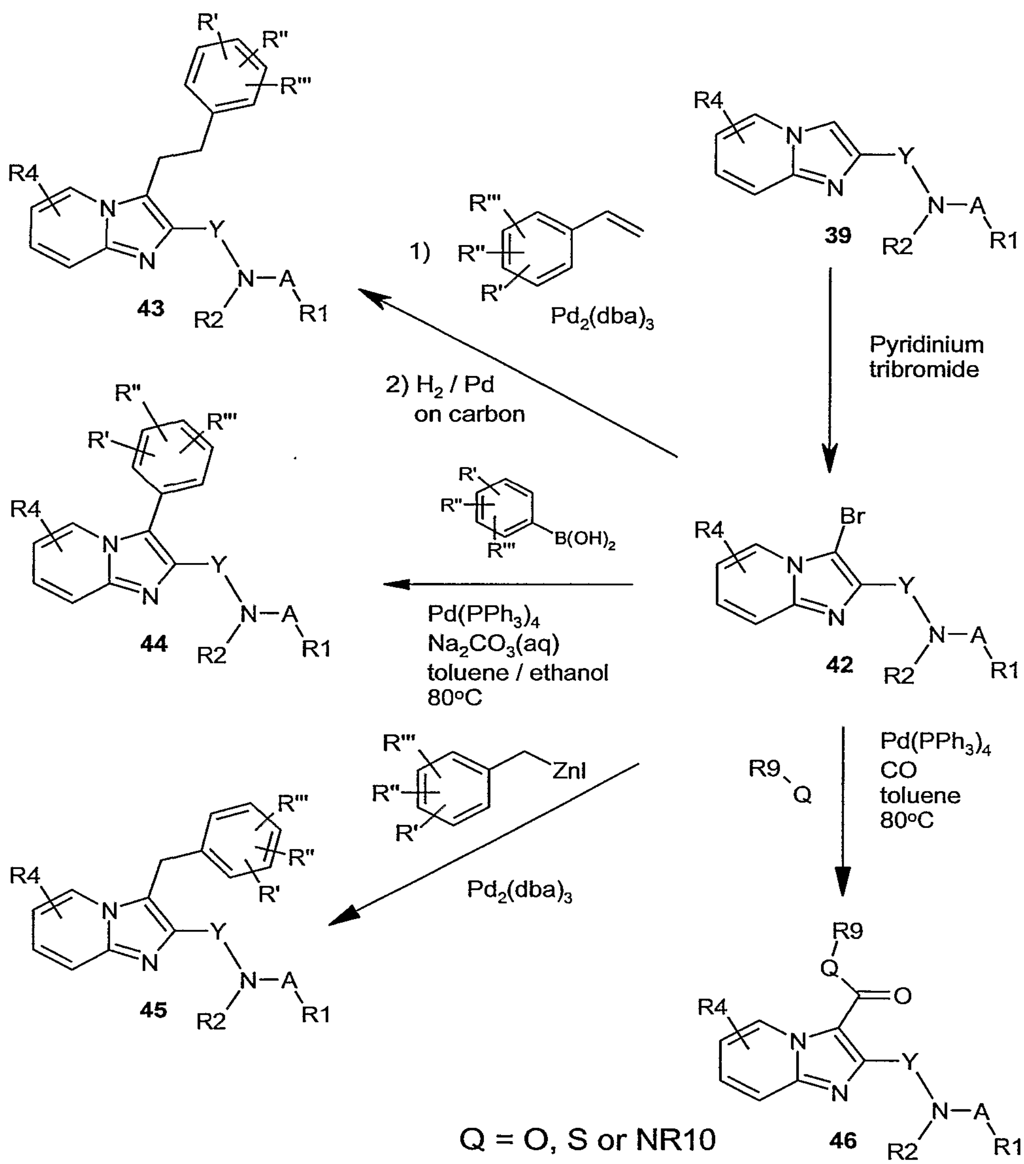


Scheme j

An isomeric series of imidazo[1,2-*a*]pyridines can be synthesised as described in Scheme j. Condensation of a suitably substituted 2-aminopyridine **1**, under the general conditions described above, with a ketone bearing two leaving groups α to the carbonyl (**36**) yields an imidazo[1,2-*a*]pyridine such as **37**. The substituted amino group can be

installed by direct alkylation to yield **39**, or by an indirect multistep route as shown above in scheme j (compound **37** to compound **38** via intermediate **39**), both routes are analogous to those shown in Schemes e.

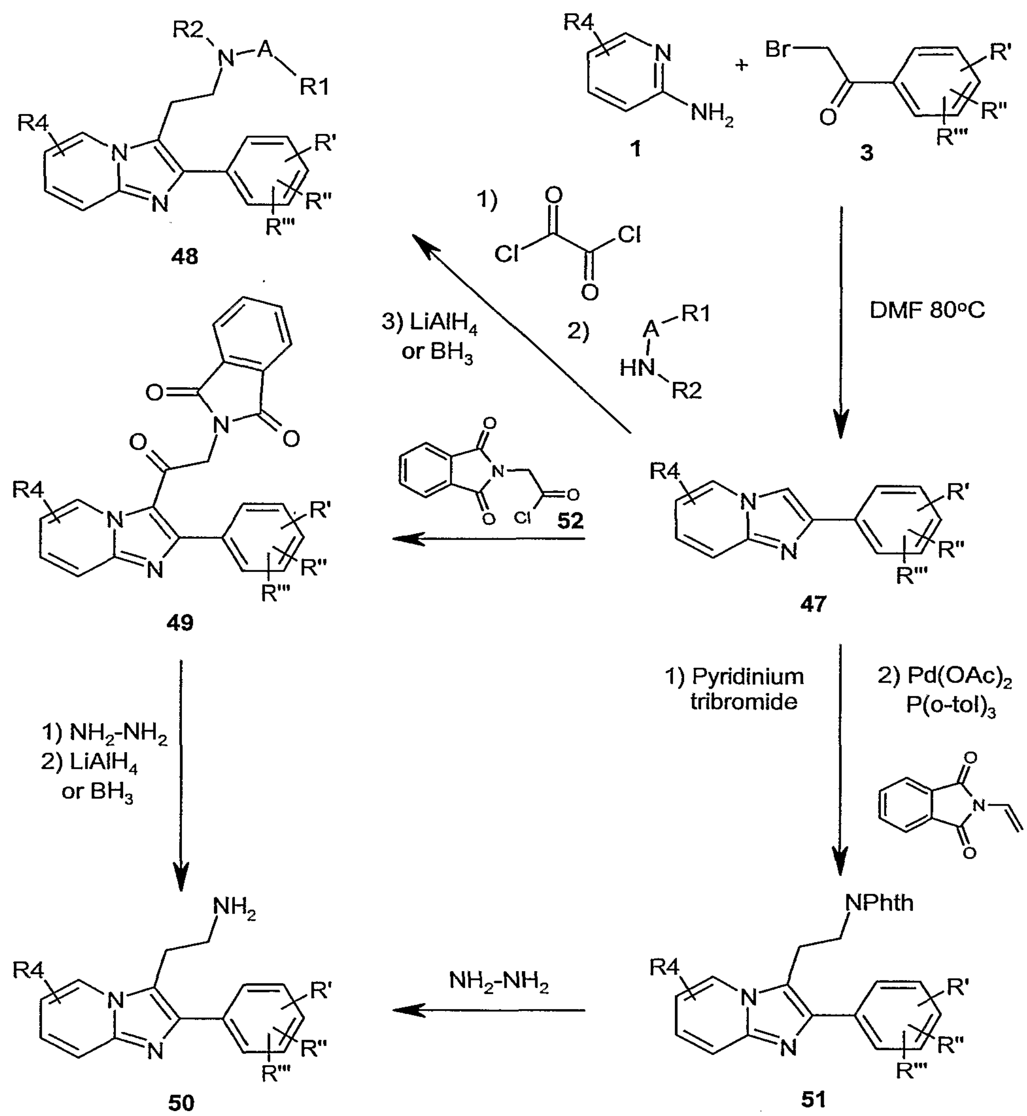
In addition the amine group can be elaborated further to a cyano-guanidine **40** or a nitroethylene moiety such as compound **41** by the same methods as described in Scheme e.



Scheme k.

Treatment of the imidazo[1,2-*a*]pyridine **39** with molecular bromine, pyridinium tribromide, poly (vinyl pyridinium tribromide) or pyrrolidone hydrobromide in an inert solvent such as chloroform or methylene chloride at -10 °C to 25 °C installs a bromo group at the two position (**42**). The compound QR9 is suitable for palladium (0) catalysed reactions, for example treatment with carbon monoxide at 1 atm or higher pressure in the

presence of a substituted amine (Q=NR10), alcohol (Q=O) or thiol (Q=S) in an inert solvent such as toluene, benzene, dioxane, THF and the like, yields 5-carbonyl-2-aryl-3-aminomethylimidazo[1,2-*a*]pyridines such as **46**. Again, treatment under palladium(0) catalysis with a weak base such aqueous sodium carbonate and the like and a substituted aryl boronic acid from commercial sources or prepared (as described in: Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y.,-H *Chem. Sci.* **1986**, *26*, 311-314.) in an inert solvent such as toluene, benzene, dioxane, THF and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours to give the imidazo[1,2-*a*]pyridine **44**. Similarly coupling of an arylalkylzinc iodide with **42** can be achieved using the method of Negishi (e.g. Jackson, R. F. W.; James, H.; Wythes, M. J.; Wood, A. *J. Chem. Soc. Chem. Commun.* **1989**, 644) yields imidazo[1,2-*a*]pyridines (**45**). Finally a Heck coupling reaction can be achieved using palladium (0) and a vinyl substituted aromatic compound in the presence of an organic amine base such as triethylamine and the like, in an inert solvent such as toluene, benzene, dioxane, THF and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours to give the imidazo[1,2-*a*]pyridine **43**.



Scheme m.

Condensation of a suitable substituted 2-aminepyridine **1** with a bromoacetophenone **3** under the described conditions above, yields imidazo[1,2-*a*]pyridines such as **47**. A ethylamine group can be installed in several ways to yield compounds described by structure **50**. Reaction **47** with oxalylchloride in an inert solvent such as dichloromethane, 1,2-dichloroethane, benzene, toluene, tetrahydrofuran and mixtures thereof and the like, at a temperature between 0°C and 100°C, with or without the presence of an organic base, such as triethylamine, pyridine and the like, yields and acid chloride, which may be reacted *in-situ* by treatment with and appropriately substituted amine [HN(R2)-A-R1] in the

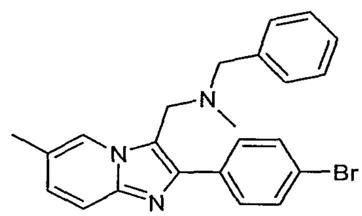
presence of an organic base such as triethylamine, pyridine and the like. The amide product from this step can then be reduced by an appropriate hydride reducing agent such as lithium aluminium hydride or borane in an appropriate inert solvent such as dichloromethane, 1,2-dichloroethane, benzene, toluene, tetrahydrofuran, thus, a fully substituted compound such as **48** can be synthesised.

Treatment of **47** with acid chloride **52** [prepared as described by Hubschwerlen, C,; Specklin, J.-L; *Org. Synth.* **1993**, *73*, 14] in an inert solvent such as dichloromethane, 1,2-dichloroethane, benzene, toluene, tetrahydrofuran and mixtures thereof and the like, at a temperature between 0°C and 100°C, with or without the presence of an organic base, such as triethylamine, pyridine and the like, yields the imidazo[1,2-*a*]pyridines **49**. Removal of the phthalimide protecting group by treatment with hydrazine, then reduction of the carbonyl group by an appropriate hydride reducing agent, such as lithium aluminium hydride or borane, in an appropriate inert solvent such as dichloromethane, 1,2-dichloroethane, benzene, toluene, tetrahydrofuran, yields the amine **50**, which may then be elaborated as shown in the earlier schemes.

Reaction of imidazo[1,2-*a*]pyridines **47** with a bromine source such as pyridinium tribromide or pyrrolidone hydrobromide in an inert solvent such as chloroform or methylene chloride at -10 °C to 25 °C, yields 3-bromo substituted imidazo[1,2-*a*]pyridines, which in turn can be treated with *N*-vinylphthalimide using Heck coupling conditions of palladium (0) catalysis in the presence of an organic amine base such as triethylamine and the like, in an inert solvent such as toluene, benzene, dioxane, THF and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours to give the imidazo[1,2-*a*]pyridine **51**. Finally treatment with hydrazine under standard conditions yields the 3-ethylamine imidazo[1,2-*a*]pyridine **50**, which again may be elaborated as shown in the earlier schemes.

EXAMPLES

Example A1 - Preparation of *N*-Benzyl-*N*-methyl-2-(4-bromophenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine.



Step A1: 2-(4-bromophenyl)-5-methyl-imidazo[1,2-*a*]pyridine.

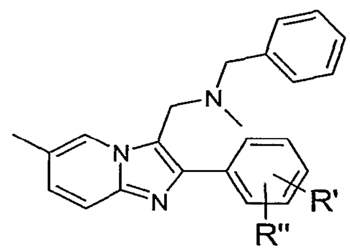
A mixture of 2-amino-5-picoline (2.00 g 18.5 mmol) and 2,4'-dibromoacetophenone (5.10 g 18.5 mmol) in DMF (20 mL) was heated at 80 °C for 1h 45 min. The mixture was cooled to RT then diluted with water (200 mL) and basified with 2M NaOH (aq) (150 mL). The mixture was extracted into EtOAc (2 × 200mL) and the extracts dried ($MgSO_4$) and concentrated *in vacuo* to give the crude title compound as a yellow solid (5.12 g 96%).
Mass Spectrum: m/e $C_{14}H_{12}BrN_2$ (M+H) 287.37 and 289.38 found.
^{1}H NMR spectrum (DMSO-d_6): δ ^{1}H NMR (300 MHz, D6 -DMSO) 2.27 (3H, s); 7.11 (1H, d); 7.48 (1H, d); 7.61 (2H, d); 7.90 (2H, d); 7.94 (1H, s); 8.32 (1H, s).

Step A2: *N*-Benzyl-*N*-methyl-2-(4-bromophenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine.

A mixture of 2-(4-bromophenyl)-5-methyl-imidazo[1,2-*a*]pyridine(4.96 g 17.3 mmol), paraformaldehyde (518 mg 17.3 mmol) and benzylmethylamine(2.23 mL 17.3mmol) in acetic acid (9 mL) was heated for 2h at 60 °C. The majority of the solvent was removed *in vacuo* and the mixture rediluted with EtOAc (400 mL) and washed with 2M NaOH (aq) (2 × 150mL). The solution was dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatograpy (silica gel, slow gradient neat CH_2Cl_2 to 6% MeOH) gave the title

compound as an orange oil (3.86 g 53%). HCl salt of title compound was prepared by the addition of 1.0M HCl in diethyl ether (23 mL) to a solution of the title compound in EtOAc (4 mL). The salt was precipitated with diethyl ether and collected by centrifuge.

Following a procedure similar to that described in Example 1, the following compounds were prepared.

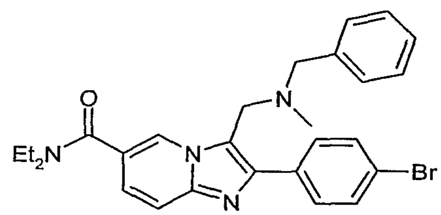


Example No.	R'	R"	δ 1H NMR (300 MHz D6-DMSO)	m/e (ESP+) (MH+)
A1 **N-Benzyl-N-methyl-2-(4-bromophenyl)-3-methylamino-5-methylimidazo[1,2-a]pyridine.**	4-Br	H	2.04 (3H, s); 2.31 (3H, s); 3.52 (2H, s); 3.96 (2H, s); 7.15 (1H, d); 7.20 - 7.30 (5H, m); 7.49 (1H, d); 7.63 (2H, d); 7.84 (2H, d); 8.31 (1H, s).	420 422
A2 **N-Benzyl-N-methyl-2-(4-chlorophenyl)-3-methylamino-5-methylimidazo[1,2-a]pyridine**	4-Cl	H		362 364
A3	4-F	H	2.40 (3H, s), 2.47 (3H, s),	360

N-Benzyl-N-methyl-2-(4-fluorophenyl)-3-methylamino-5-methylimidazo[1,2-a]pyridine			4.20 (1H, s), 4.55 (1H, s), 5.00 (2H, s), 7.38-7.57 (6H, m), 7.86-7.97 (m, 4H), 9.15 (0.5H, s) and 11.64 (0.5H, s).	
A4 **N-Benzyl-N-methyl-2-(4-cyanophenyl)-3-methylamino-5-methylimidazo[1,2-a]pyridine**	4-CN	H	2.41 (3H, s), 2.44 (3H, s), 4.23 (1H, s), 4.53 (1H, s), 5.02 (2H, s), 7.43 (3H, s), 7.54 (2H, s), 7.73 (1H, d), 7.85 (1H, d), 8.02 (4H, s), 8.92 (0.5H, s) and 11.17 (0.5H, s).	367
A5 **N-Benzyl-N-methyl-2-(4-methoxyphenyl)-3-methylamino-5-methylimidazo[1,2-a]pyridine**	4-OMe	H	2.40 (3H, s), 2.47 (3H, s), 3.86 (3H, s), 4.20 (1H, s), 4.54 (1H, s), 5.00 (2H, s), 7.16 (2H, d), 7.42 (3H, s), 7.55 (2H, s), 7.75 (2H, d), 7.91 (2H, s), 9.05 (0.5H, s) and 11.47 (0.5H, s).	372
A6 **N-Benzyl-N-methyl-2-(3,4-dimethoxyphenyl)-3-methylamino-5-methylimidazo[1,2-a]pyridine**	4-OMe	3-OMe	2.39 (3H, s), 2.48 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 4.24 (1H, s), 4.57 (1H, s), 5.03 (2H, s), 7.14 (1H, d), 7.37 (2H, d), 7.41 (3H, s), 7.92 (2H, s), 9.08 (0.5H, s) and 11.50 (0.5H, s).	402
A7 **N-Benzyl-N-methyl-2-(3,4-dichlorophenyl)-3-**	4-Cl	3-Cl	2.37 (3H, s), 2.46 (3H, s), 4.12 (1H, s), 4.54 (1H, s), 4.70 (2H, s), 4.87 (1H, s),	410 412

methylamino-5-methylimidazo[1,2-*a*]pyridine			7.42 (3H, s), 7.53 (2H, S), 7.67 (1H, d), 7.70 (1H, d), 7.85 (1H, d), 7.94 (2H, s), 9.06 (0.5H, s) and 11.44 (0.5H, s).	

Example B1 - Preparation of *N*-Benzyl-*N*-methyl-2-(4-bromophenyl)-5-diethylamido-3-methylamino-imidazo[1,2-*a*]pyridine.



Step B1: **2-(4-bromophenyl)-5-carboxy-imidazo[1,2-*a*]pyridine.**

A mixture of 6-aminonicotinic acid (1.00 g 7.24 mmol) and 2,4'-dibromoacetophenone (4.02 g 14.5 mmol) in DMF (10 mL) was heated at 60 °C for 24 h. The mixture was cooled to RT then partitioned between water (200 mL) and EtOAc (250mL). The yellow precipitate between the two layers was removed by filtration and dried by high vacuum to yield the title compound (1.72 g 75%).

Mass Spectrum: m/e $C_{14}H_{10}BrN_2O_2$ (M+H) 317.16 and 319.16 found.

Step B2: **2-(4-bromophenyl)-5-diethylamido-imidazo[1,2-*a*]pyridine.**

HOBt (426 mg 3.15mmol) was added in one portion to a stirred solution of 2-(4-bromophenyl)-5-carboxylic-imidazo[1,2-*a*]pyridine (1.00 g 3.15 mmol) and EDC (605 mg 3.15 mmol) in CH_2Cl_2 (30 mL) under N_2 at O°C. The mixture was stirred for 1h then diethylamine (1.63 mL 15.8 mmol) was added and the mixture allowed to stir at RT for 20h. After this time the solvent was removed *in vacuo* then the mixture rediluted with EtOAc (250 mL) then washed with 1M citric acid (200 mL) then saturated $NaHCO_3$ (aq) (200 mL) and brine (200 mL). The organic solution was dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a yellow solid (601 mg 51%).

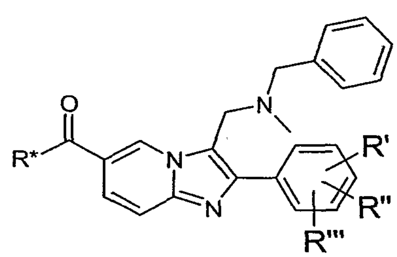
Mass Spectrum: m/e $C_{18}H_{18}BrN_2O_2$ (M+H) 272.20 and 274.23 found.

^{1}H NMR spectrum (DMSO-d_6): δ ^{1}H NMR (300 MHz, D6 -DMSO) 1.15 (6H, t), 3.18 (4H, m); 7.12 (1H, d); 7.30 (1H, d); 7.33 (2H, d); 7.93 (2H, d); 8.44 (1H, s); 8.68 (1H, s).

Step B3: **N-Benzyl-N-methyl-2-(4-bromophenyl)-5-diethylamido-3-methylamino-imidazo[1,2-a]pyridine.**

A mixture of 2-(4-bromophenyl)-5-diethylamido-imidazo[1,2-*a*]pyridine (300 mg 0.806 mmol), paraformaldehyde (26.0 mg 0.812 mmol) and benzylmethylamine(100 μL 0.806 mmol) in acetic acid (2 mL) was heated for 1h at 50°C. The majority of the solvent was removed *in vacuo* and the mixture rediluted with EtOAc (200 mL) and washed with 2M NaOH (aq) (2 × 150mL). The solution was dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatograpy (silica gel, slow gradient neat CH_2Cl_2 to 6% MeOH) gave the title compound as an yellow oil (276 mg 68%). HCl salt of title compound was prepared by the addition of 1.0M HCl in diethyl ether (150 μL) to a solution of the title compound in EtOAc (500 μL). The salt was precipitated with diethyl ether and collected by centrifuge.

Following a procedure similar to that described in Example 1, the following compounds were prepared.

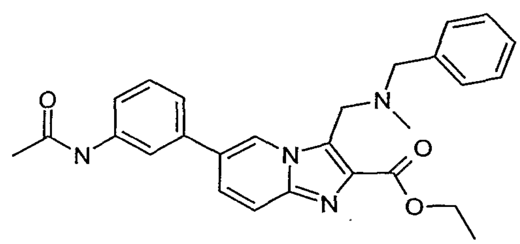


Example No.	R'	R"	R'''	R*	δ 1H NMR (300 MHz, D6 - DMSO)	m/e (M+H)
B1	4-Br	H	H	Et_2N	1.05 - 1.13 (6H, b);	505

N-Benzyl-N-methyl-2-(4-bromophenyl)-5-diethylamido-3-methylamino-imidazo[1,2-*a*]pyridine					2.04 (3H, s); 3.39 (4H, b); 3.50 (2H, s); 4.09 (2H, s); 7.16 - 7.29 (5H, m); 7.32 (1H, d); 7.62 (1H, d); 7.70 (2H, d); 7.86 (2H, d); 8.58 (1H, s).	507
B2 **N-Benzyl-N-methyl-2-(4-bromophenyl)-5-isopropyloxycarbonyl-3-methylamino-imidazo[1,2-*a*]pyridine**	4-Br	H	H	*i*PrO	1.20 (6H, d); 1.98 (3H, s); 3.59 (2H, b); 4.15 (2H, s); 7.21 - 7.33 (5H, m); 7.62 - 7.74 (4H, m); 7.75 - 7.83(4H, m); 9.25 (1H, s).	492 494
B3 **N-Benzyl-N-methyl-2-(4-isopropylamidophenyl)-5-isopropyloxycarbonyl-3-methylamino-imidazo[1,2-*a*]pyridine**	4-NH C(O)*i*Pr	H	H	*i*PrO	1.12 (6H, d); 1.38 (6H, d); 1.97 (3H, s); 2.64 (1H, 'q'); 3.57 (2H, s); 4.16 (2H, s); 5.21 (1H, 'q'); 7.20 - 7.32 (5H, m); 7.63 (1H, d); 7.70 (1H, d); 7.75(4H, 's'); 9.28 (1H, s); 9.92 (1H, s).	499
B4 **N-Benzyl-N-methyl-2-(3,4,5-trimethylphenyl)-5-diethylamido-3-methylamino-imidazo[1,2-*a*]pyridine**	3-Me,	Me	4-Me	Et_2N	1.16 (6H, b); 2.20 (3H, s); 2.26 (3H, s); 2.37 (6H, s); 3.48 (4H, b); 3.54 (2H, s); 4.04 (2H, s); 7.18 - 7.32 (6H, m); 7.46 (2H, s);	469

					7.63 (1H, d); 8.58 (1H, s).	

Example C - Preparation of Ethyl *N*-benzyl-*N*-methyl-5-(3-acetamidophenyl)-3-methylamino-imidazo[1,2-*a*]pyridine-2-carboxylate.



Step C1: **Ethyl 5-bromo-imidazo[1,2-*a*]pyridine-2-carboxylate.**

A mixture of 2-amino-5-bromopyridine (1.00 g 5.78 mmol) and ethyl bromopyruvate (0.730 mL 5.78 mmol) in DMF (10 mL) was heated at 80 °C for 2 h. The mixture was cooled to RT then partitioned between water (200 mL) and EtOAc (250mL). The aqueous layer was extracted again with EtOAc (2 × 100mL) and the combined extracts dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude title compound as a yellow solid (1.24 g 80%).

Mass Spectrum: m/e $C_{10}H_9BrN_2O_2$ (EP+) (MH+) 264 and 271 found.

^{1}H NMR spectrum (DMSO-d_6): δ ^{1}H NMR (300 MHz, D6 -DMSO) 1.31 (3H, t), 4.31 (2H, q); 7.46 (1H, d); 7.61 (1H, d); 7.33 (2H, d); 8.45 (1H, s); 8.89 (1H, s).

Step C2: **Ethyl *N*-Benzyl-*N*-methyl-5-bromo-3-methylamino-imidazo[1,2-*a*]pyridine-2-carboxylate.**

A mixture of ethyl 5-bromo-imidazo[1,2-*a*]pyridine-2-carboxylate (1.24 g 4.61 mmol), paraformaldehyde (138 mg 4.61 mmol) and benzylmethylamine(600 μL 4.61 mmol) in acetic acid (15 mL) was heated for 1h at 50 °C. The majority of the solvent was removed *in vacuo* and the mixture rediluted with EtOAc (250 mL) and washed with 2M NaOH (aq) (3 × 150mL). The solution was dried ($MgSO_4$) and concentrated *in vacuo*. Flash column

chromatograpy (silica gel, slow gradient neat CH_2Cl_2 to 10% MeOH) gave the title compound as an yellow oil (980 mg 53%).

Mass Spectrum: m/e $C_{19}H_{20}BrN_3O_2$ (EP+) (MH+) 264 and 271 found.

^{1}H NMR spectrum (DMSO-d$_6$): δ ^{1}H NMR (300 MHz, D6 -DMSO) 1.32 (3H, t); 2.08 (3H, s); 3.58 (2H, s); 4.22 (2H, s); 4.33 (2H, q); 7.21 - 7.34 (5H, m); 7.50 (1H, d); 7.59 (1H, d); 8.57 (1H, s).

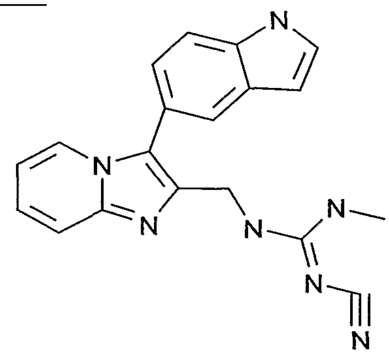
Step C3: **Ethyl *N*-benzyl-*N*-methyl-5-(3-acetamidophenyl)-3-methylamino-imidazo[1,2-*a*]pyridine-2-carboxylate.**

Tetrakis(triphenylphosphine) palladium(0) (58.0 mg 0.050 mmol) was added in one portion to a degassed mixture of ethyl *N*-Benzyl-*N*-methyl-5-bromo-3-methylamino-imidazo[1,2-*a*]pyridine-2-carboxylate (200 mg 0.498 mmol) and N-acetyl-3-aminobenzeneboronic acid (89.0 mg 0.498 mmol) in toluene (2 mL), ethanol (2 mL) and saturated $NaHCO_3$ (aq) (1 mL). The mixture was heated at 80 °C with vigorous stirring for 4 h then cooled to RT. The mixture was diluted with EtOAc (200 mL) and washed with water (100 mL) and brine (100 mL) then dried ($MgSO_4$). The solution was concentrated in vacuo and the product isolated by flash column chromatography (3 runs on silica slow gradient neat CH_2Cl_2 to 20% MeOH). This gave the title compound as a colourless oil (27.0 mg 12%).

Mass Spectrum: m/e $C_{27}H_{28}N_4O_3$ (EP+) (MH+) 456 found.

^{1}H NMR spectrum (DMSO-d$_6$): δ ^{1}H NMR (300 MHz, $CDCl_3$) 1.46 (3H, t); 2.21 (3H, s); 2.25 (3H, s); 3.61 (2H, s); 4.23 (2H, s); 4.48 (2H, q); 7.15 - 7.29 (5H, m); 7.29 - 7.37 (1H, m); 7.38 - 7.49 (3H, m); 7.76 (1H, s); 7.89 (1H, s); 8.39 (1H, s). HCl salt of title compound was prepared by the addition of 1.0M HCl in diethyl ether (177 µL) to a solution of the title compound in EtOAc (300 µL). The salt was precipitated with diethyl ether and collected by centrifuge.

Example D1 - Preparation of *N*-Cyano-*N'*-[3-(1H-indol-5-yl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N''*-methyl-guanidine



Step D1: Preparation of 1-Imidazo[1,2-a]pyridin-2-ylmethyl-3-cyano-2-phenyl-isourea

A mixture of 2-aminomethylimidazo[1,2-*a*]pyridine (1.20 g, 9.00 mmol) and diphenyl-cyanocarbonimidate (2.35 g, 9.90 mmol) in IPA were stirred at ambient temperature for 4 h. The cloudy reaction gave rise to a precipitate which was filtered. This was washed with ether and dried to yield the title compound as a white solid (1.55 g, 59 %). **Mass Spectrum:** 292 [MH]+

Step D2: Preparation of *N*-Cyano-*N'*-(imidazo[1,2-*a*]pyridin-2-ylmethyl)-*N''*-methyl-guanidine

A mixture of 1-imidazo[1,2-*a*]pyridin-2-ylmethyl-3-cyano-2-phenyl-isourea (1.00 g, 3.40 mmol) and excess methylamine in 33% aq. ethanol (5 mL) in IPA were warmed to 70 °C for 2 h. The reaction was concentrated *in vacuo*, and the residue triturated with ethyl acetate and filtered. The resulting solid was washed with ether and dried to give the title compound as a white solid (0.75 g, 97%).

Mass Spectrum: 229 [MH]+

^{1}H NMR spectrum (DMSO-d$_6$): 2.72 (3H, s); 4.40 (2H, s); 6.82 (1H, t); 7.17 (1H, brs), 7.19 (1H, t); 7.40 (1H, br s); 7.48 (1H, d); 7.78 (1H, s); 8.48 (1H, d).

Step D3: **<u>*N*-Cyano-*N'*-(3-bromo-imidazo[1,2-*a*]pyridin-2-ylmethyl)-*N''*-methyl-guanidine</u>**

A mixture of *N*-Cyano-*N'*-(imidazo[1,2-*a*]pyridin-2-ylmethyl)-*N''*-methyl-guanidine (0.300 g, 1.30 mmol), poly(4-vinylpyridinium tribromide) (0.467 g, 1.40 mmol), pyridine (2 drops) in CH_2Cl_2 were stirred at ambient temperature for 16 h. DMF was added, the solid support filtered off, and the mother liquors concentrated *in vacuo*. The residue was triturated with CH_2Cl_2 and the resulting solid filtered to yield the title compound as a fawn solid (0.390 g, 98%).

<u>Mass Spectrum:</u> 307, 309 [MH]+

<u>^{1}H NMR spectrum (DMSO-d_6):</u> 2.76 (3H, d); 4.46 (2H, d); 7.21 (1H, d); 7.24 (1H, t); 7.45 (1H, t); 7.58 (1H, t); 7.76 (1H, d); 8.45 (1H, d)

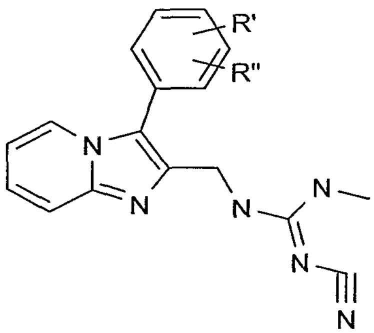
Step D4: **<u>Preparation of *N*-Cyano-*N'*-[3-(1H-indol-5-yl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N''*-methyl-guanidine</u>**

To a mixture of *N*-Cyano-*N'*-(3-bromo-imidazo[1,2-*a*]pyridin-2-ylmethyl)-*N''*-methyl-guanidine (700 mg, 0.230 mmol), 5-indolyl boronic acid (560 mg, 0.345 mmol), saturated Na_2CO_3 (1.5 mL), ethanol (0.60 mL) and toluene (3 mL) was added a catalytic amount of $Pd(PPh_3)_4$. The reaction was stirred at 80 °C for 16 h. The reaction was poured onto a hydromatrix column and eluted with CH_2Cl_2. Flash column chromatography (silica gel, slow gradient, neat CH_2Cl_2 to 5% MeOH:CH_2Cl_2) gave the title compound as a white solid (17.0 mg, 22%).

<u>Mass Spectrum:</u> 344 [MH]+

<u>^{1}H NMR spectrum (DMSO-d_6):</u> 2.89 (3H, d); 4.02 (2H, d); 5.85 (1H, t); 6.63 (1H, s); 6.88 (1H, t); 7.17- 7.27 (3H, m); 7.36 (1H , m); 7.57 (1H, d); 7.59 (1H, d); 7.66 (1H, s), 8.08 (1H, d); 8.78 (1H, br s)

Following a procedure similar to that described for Example D1, the following compounds were prepared.



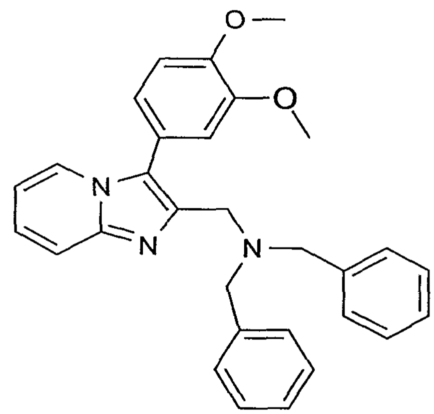
Example No.	R'	R"	^{1}H NMR spectrum (DMSO-d_6):	Mass Spectrum [MH]+
D2	3-OMe	4-OMe	2.71(3H, d); 3.80 (3H, s); 3.86 (3H, s); 4.55 (2H, d); 7.21 (2H, s); 7.28 (2H, s) ; 7.43 (1H, t); 7.65 (1H, t); 7.90-8.03 (2H, m); 8.50 (1H, d)	365
D3	4-Cl		2.69 (3H, d); 4.54 (2H, d); 7.30 (1H, d); 7.45 (1H, t); 7.73 (4H, s); 7.92-8.08 (3H, m); 8.52 (1H, d)	339
D4	3-Me	5-Me	2.41 (6H, s); 2.92 (3H, d); 4.42 (2H, d); 5.78 (1H, t); 6.81 (1H, t); 7.03 (2H, s); 7.15 (1H, s); 7.22 (2H, t); 7.57 (1H, d); 8.04 (1H, d)	333

D2 = *N*-Cyano-*N'*-[3-(3,4-dimethoxyphenyl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N''*-methyl-guanidine

D3 = *N*-Cyano-*N'*-[3-(4-chlorophenyl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N''*-methyl-guanidine

D4 = *N*-Cyano-*N'*-[3-(3,5-dimethylphenyl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N''*-methyl-guanidine

Example E - *N,N*-Dibenzyl-2-methylamino-3-(3,4-dimethoxyphenyl)imidazo[1,2-*a*]pyridine



Step E1: Preparation of *N,N*-Dibenzyl-2-methylaminoimidazo[1,2-*a*]pyridine

A mixture of 2-aminoethylimidazo[1,2-*a*]pyridine dihydrochloride (0.500 g, 2.26 mmol), benzyl bromide (0.430 g, 2.50 mmol) and powdered K_2CO_3 (1.56 g, 11.3 mmol) in DMF (20 mL) was heated at 100 °C for 2 h. The DMF was removed *in vacuo* and then residue taken into CH_2Cl_2 and filtered to remove inorganics. This was purified by flash column chromatography (silica gel, CH_2Cl_2 to 5% MeOH:CH_2Cl_2) to give the title compound as orange oil (0.405 g, 55%).

Mass Spectrum: 328 [MH]+

^{1}H NMR spectrum ($CDCl_3$): 3.68 (4H, s); 3.82 (2H, s); 6.74 (1H, t); 7.10 (1H, t); 7.18-7.48 (10H, m); 7.55 (1H, d); 7.60 (1H, s); 8.07 (1H, d)

Step E2: Preparation of *N,N*-Dibenzyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine

A mixture of *N,N*-Dibenzyl-2-methylaminoimidazo[1,2-*a*]pyridine (0.380 g, 1.16 mmol), poly(4-vinylpyridinium tribromide) (0.387 g, 1.16 mmol), pyridine (2 drops) in CH_2Cl_2 (20 mL) were stirred at ambient temperature for 16 h. The solid support was filtered off

and the mother liquors concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, slow gradient, CH_2Cl_2 to 3:7 EtOAc:Hexane to 6:4 EtOAc:Hexane) to yield the title compound as a yellow oil (0.260 g, 55%).

Mass Spectrum: 406, 408 [MH]+

^{1}H NMR spectrum ($CDCl_3$): 3.70 (4H, s); 3.82 (2H, s); 6.90 (1H, t); 7.17-7.48 (11H, m); 7.58 (1H, d), 8.08 (1H, d)

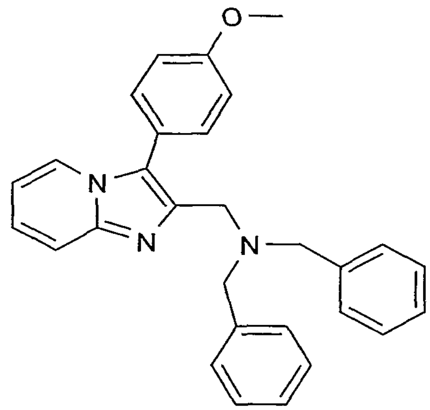
Step E3: Preparation of *N,N*-Dibenzyl-2-methylamino-3-(3,4-dimethoxyphenyl)imidazo[1,2-*a*]pyridine

To a mixture of *N,N*-Dibenzyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine (150 mg, 0.370 mmol), 3,4-dimethoxybenzene boronic acid (81.0 mg, 0.440 mol), saturated Na_2CO_3 (2.5 mL), ethanol (0.90 mL) and toluene (4.50 mL), was added a catalytic amount of $Pd(PPh_3)_4$. The reaction was stirred at 80 °C for 3 h. The toluene layer was separated and concentrated *in vacuo*. Flash column chromatography (silica gel, slow gradient, neat CH_2Cl_2 to 3:7EtOAc:Hexane to 7:3 EtOAc:Hexane) gave the title compound as an oil. The HCl salt was prepared by addition of 1M HCl in diethyl ether to a solution of the compound in EtOAc to give the title compound dihydrochloride as a white solid (98.0 mg, 49%).

Mass Spectrum: 464 [MH]+

^{1}H NMR spectrum (DMSO-d_6): 3.75 (3H, s); 3.88 (3H, s); 4.08 (4H, br s); 4.15 (2H, brs); 7.05-7.19 (3H, m); 7.30 (7H, s); 7.46 (4H, s); 7.84 (1H, t); 8.00 (1H, d); 8.43 (1H, d)

Example F - <u>Preparation of *N,N*-Dibenzyl-2-methylamino-3-(4-dimethoxyphenyl)imidazo[1,2-*a*]pyridine</u>

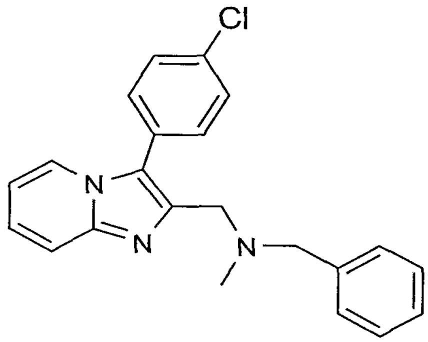


To a mixture of *N,N*-Dibenzyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine (100mg, 0.25mmol), 4-methoxybenzene boronic acid (76.0 mg, 0.500 mol), saturated Na_2CO_3 (1.5 mL), ethanol (0.6 mL) and toluene (3 mL), was added a catalytic amount of $Pd(PPh_3)_4$. The reaction was stirred at 80 °C for 3 h.

The toluene layer was separated and concentrated *in vacuo*. Flash column chromatography (silica gel, slow gradient, neat CH_2Cl_2 to 3:7 EtOAc:Hexane to 7:3 EtOAc:Hexane) gave the title compound as an oil. The HCl salt was prepared by addition of 1M HCl in diethyl ether to a solution of the compound in EtOAc to give the title compound dihydrochloride as a white solid (41.0 mg, 32%)

<u>Mass Spectrum:</u> 434 [MH]+

Example G - Preparation of *N*-benzyl-*N*-methyl-2-methylamino-3-(4-chlorophenyl)imidazo[1,2-*a*]pyridine



Step G1: Preparation of 2-chloromethylimidazo[1,2-*a*]pyridine

A mixture of dichloroacetone (17.8 g, 14.0 mmol) and 2-aminopyridine (10.0 g , 11.0 mmol) in DMF (80 mL) was stirred at ambient temperature for 5 h. The resulting precipitate was filtered off and washed with DMF and then diethyl ether. This solid was then taken up in DMF (100 mL), 4A molecular sieves added and the reaction stirred at 80 °C for 3 h. The resulting precipitate was filtered off and washed with diethyl ether to yield the title compound as a white solid.

Mass Spectrum: 167 [MH]+

^{1}H NMR spectrum (DMSO-d_6): 5.11 (2H, s); 7.48 (1H, t); 7.95 (2H, s); 8.49 (1H, s); 8.97 (1H, d).

Step G2: Preparation of *N*-benzyl-*N*-methyl-2-methylaminoimidazo[1,2-*a*]pyridine

A mixture of 2-chloromethylimidazo[1,2-*a*]pyridine (2.00 g, 12.0 mmol), *N*-methylbenzylamine (1.75 g, 14.5 mmol) and powdered K_2CO_3 (3.30 g, 2.40 mmol) in DMF (50 mL) was heated at 90 °C for 4 h. After cooling, the inorganics were filtered off and the filtrate evaporated *in vacuo*. Purification by flash column chromatography (silica gel,

slow gradient, CH_2Cl_2 to 5% MeOH:CH_2Cl_2) gave the title compound as a yellow oil (1.42 g, 48%).

Mass Spectrum: 252 [MH]+

^{1}H NMR spectrum (DMSO-d$_6$): 2.30 (3H, s); 3.63 (2H, s); 3.79 (2H, s); 6.73 (1H, t); 7.11 (1H, t); 7.20-7.42 (5H, m); 7.55 (1H, s); 7.57 (1H, d); 8.06 (1H,d)

Step G3: Preparation of *N*-benzyl-*N*-methyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine

A mixture of *N*-benzyl-*N*-methyl-2-methylaminoimidazo[1,2-*a*]pyridine (1.30 g, 5.20 mmol), poly(4-vinylpyridinium tribromide) (1.82 g, 5.50 mmol) and pyridine (2 drops) in CH_2Cl_2 (20 mL) were stirred at ambient temperature for 16 h. A further portion of poly (4-vinylpyridinium tribromide) (0.400 g, 1.20 mmol) was added and the reaction stirred for a further 16 h. DMF was added, the solid support filtered off, and the mother liquors concentrated *in vacuo*. The residue was triturated with diethyl ether, and filtered to yield the title compound as a cream solid (1.85 g, 99%).

Mass Spectrum: 330, 332 [MH]+

^{1}H NMR spectrum (DMSO-d$_6$): 2.77 (3H, s); 4.39 (2H, s); 4.43 (2H, br s); 7.16 (1H, t); 7.42-7.50 (4H, m); 7.55-8.00 (2H, m); 7.69 (1H, d); 8.40 (1H, d)

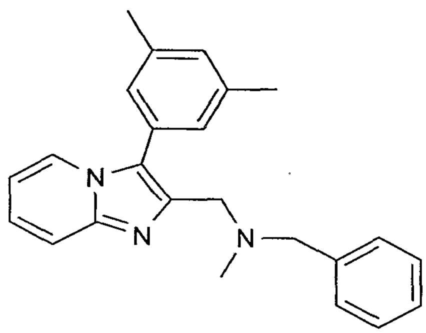
Step G4: Preparation of *N*-benzyl-*N*-methyl-2-methylamino-3-(4-chlorophenyl)imidazo[1,2-*a*]pyridine

To a mixture of *N*-benzyl-*N*-methyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine (200 mg, 0.60 mmol), 4-chlorobenzeneboronic acid (141 mg, 0.910 mmol) and saturated Na_2CO_3 (3 mL) in ethanol (1.2 mL) and toluene (6 mL) was added a catalytic amount of $Pd(PPh_3)_4$. The reaction was stirred at 80 °C for 16 h. The reaction was poured onto a hydromatrix column and eluted with CH_2Cl_2. Flash column chromatography (silica gel, slow gradient, neat CH_2Cl_2 to 5% MeOH:CH_2Cl_2) gave an oil. The HCl salt was prepared by addition of 1M HCl in diethyl ether to a solution of the compound in EtOAc to give the title compound as the dihydrochloride as a white solid (26mgs, 10%).

Mass Spectrum: 362 [MH]+

^{1}H NMR spectrum (DMSO-d_6): 2.72 (3H, s); 4.28 (2H, brs); 4.38 (2H, s); 7.18 (1H, t); 7.35-7.41 (3H, m); 7.50-7.57 (2H, m); 7.63 (5H ,s); 7.51 (1H, d); 8.34 (1H,d)

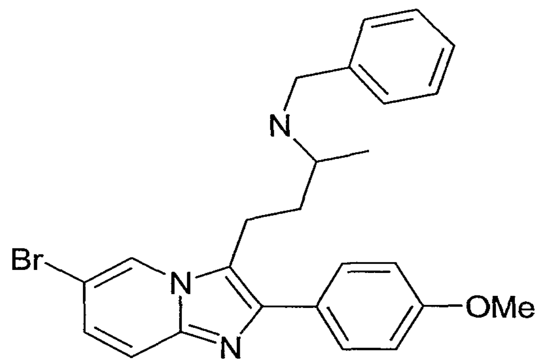
Example H: Preparation of *N*-benzyl-*N*-methyl-2-methylamino-3-(3,5-dimethylphenyl)imidazo[1,2-*a*]pyridine



To a mixture of *N*-benzyl-*N*-methyl-2-methylamino-3-bromoimidazo[1,2-*a*]pyridine (100 mg, 0.400 mmol), 3,5-dimethylbenzene boronic acid (89.0 mg, 0.600 mmol), and sodium carbonate (2 mL) in dioxan (4 mL) was added a catalytic amount of $Pd(PPh_3)_4$. The reaction was stirred at 90 °C for 16 h, then evaporated *in vacuo*. Purification by flash column chromatography (silica gel, slow gradient, neat CH_2Cl_2 to 5% MeOH:CH_2Cl_2) gave an oil. The HCl salt was prepared by addition of 1M HCl in diethyl ether to give the title compound dihydrochloride as a white solid (50.0 mg, 29%).

Mass Spectrum: 356 [MH]+

Example J: **Preparation of *N*-Benzyl-5-bromo-3-(3-methylpropylamino)-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine**



Step J1: **5-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine**

2-amino-5-bromopyridine (5.00 g, 28.9 mmol) was added to a solution of 2-bromo-4-methoxyacetophenone (6.62 g, 28.9 mmol) in DMF (50 mL), and the reaction stirred at 80 °C for 2h. The reaction mixture was partitioned between 1M NaOH (200 mL) and ethyl acetate (200 mL), upon which the majority of the product precipitated from solution and was filtered under vacuum. The organic layer that remained was extracted, dried over magnesium sulfate and evaporated *in vacuo* to give a yellow solid, which was combined with the above to give the title compound (6.74 g, 77%).

^{1}H NMR spectrum (DMSO-d$_6$): 3.80 (s, 3H); 7.00 (d, 2H); 7.30 (d, 1H); 7.50 (d, 1H); 7.85 (d, 2H); 8.25 (s, 1H); 8.80 (s, 1H).

Mass Spectrum: 303, 305 [MH]+

Step J2: **5-bromo-3-(3-oxo-butyl)-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine**

Methyl vinyl ketone (1.00 mL, 12.0 mmol) was added to a solution of 5-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (1.00 g 3.32 mmol) in glacial acetic acid (30 mL), followed by the addition of acetic anhydride (10 mL). The reaction was stirred at reflux for 14h. The reaction mixture was evaporated *in vacuo* and the crude product purified by

flash chromatography (silica gel, eluting from 25% ethyl acetate:hexane to 50% ethyl acetate:hexane) to give the title compound as a yellow solid (1.09 g, 88%).

^{1}H NMR spectrum (DMSO-d_6): 2.10 (s, 3H); 2.85 (t, 2H); 3.10 (t, 2H); 3.80 (s, 3H); 7.00 (d, 2H); 7.25 (d, 1H); 7.50 (d, 1H); 7.65 (d, 2H); 8.70 (s, 1H).

Mass Spectrum: 373, 375 [MH]+

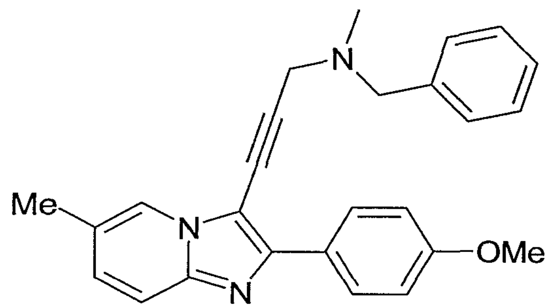
Step J3: *N*-Benzyl-5-bromo-3-(3-methylpropylamino)-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine

Under an inert atmosphere, benzylamine (0.090 mL, 0.820 mmol) was added to a solution of 5-bromo-3-(3-oxo-butyl)-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (300 mg, 0.810 mmol) and toluene sulphonic acid (1 mg, catalytic amount) in anhydrous methanol (10 mL). The reaction mixture was then allowed to reflux over molecular sieves for 16 h. Sodium borohydride (61.0 mg, 1.61 mmol) was added over a period of 30 min, and the reaction left to stir for 30 min. The reaction mixture was evaporated *in vacuo*, and purified by flash chromatography (silica gel, eluting with 1% MeOH: CH_2Cl_2 to 5% MeOH: CH_2Cl_2) to give the title compound as an oil. The hydrochloride salt was formed by addition of HCl in ether, and recrystallised from iso-propanol, to give the title compound hydrochloride as a white solid (40.0 mg, 11%).

^{1}H NMR spectrum (DMSO-d_6): 1.35 (d, 3H); 1.80-2.00 (m, 2H); 2.15-2.25 (m, 2H); 3.75 (q, 1H); 3.85 (s, 3H); 4.00-4.20 (m, 2H); 7.15 (d, 2H); 7.40 (m, 3H); 7.55 (m, 2H); 7.70 (d, 2H); 7.85-8.00 (dd, 2H); 9.20 (s, 1H); 9.45 (s, 1H).

Mass Spectrum: 464, 466 [MH]+

Example K1: Preparation of *N*-Benzyl-*N*-Methyl-5-methyl-3-propargylamino-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine



Step K1: 5-methyl-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine

2-amino-5-picoline (5.00 g, 46.3 mmol) was added to a solution of 2-bromo-4-methoxyacetophenone (10.6 g, 46.3 mmol) in DMF (50 mL), and the reaction stirred at 80 °C for 2h. The reaction mixture was partitioned between 1M NaOH (200 mL) and ethyl acetate (200 mL), upon which the majority of the product precipitated from solution and was filtered under vacuum. The organic layer that remained was extracted, dried over magnesium sulfate and evaporated *in vacuo* to give a yellow solid, which was combined with the above to give the title compound (8.20 g, 74%).

^{1}H NMR spectrum (DMSO-d_6): 2.25 (s, 3H); 3.80 (s, 3H); 6.95 (d, 2H); 7.05 (d, 1H); 7.40 (d, 1H); 7.85 (d, 2H); 8.15 (s, 1H); 8.25 (s, 1H).

Mass Spectrum: 239 [MH]+

Step K2: 5-methyl-3-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine

Poly(4-vinylpyridinium tribromide) (2.80 g, 8.40 mmol) was added to a solution of 5-methyl-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (2.00 g, 8.40 mmol) in dichloromethane, which was followed by the addition of a few drops of pyridine. The reaction was allowed to stir at room temperature for 14h. The reaction mixture was filtered by vacuum, washed with water (2 × 75 mL) and the organics separated, dried over

magnesium sulfate, filtered and evaporated *in vacuo* to give the title compound as a pale yellow solid (1.64 g, 62%).

^{1}H NMR spectrum (DMSO-d$_6$): 2.25 (s, 3H); 3.80 (s, 3H); 6.95 (d, 2H); 7.05 (d, 1H); 7.40 (d, 1H); 7.85 (d, 2H); 8.15 (s, 1H).

Mass Spectrum: 317, 319 [MH]+

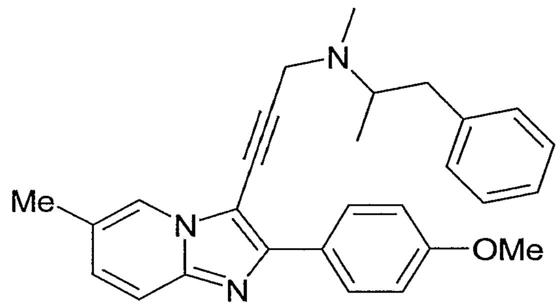
Step K3: *N*-Benzyl-*N*-Methyl-5-methyl-3-propargylamino-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine

Pargyline hydrochloride (202 mg, 1.26 mmol) was added to a solution of 5-methyl-3-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (20mg, 0.63mmol) in diethylamine (15 mL), and the solution bubbled with nitrogen. Copper Iodide (12.0 mg, 0.060 mmol) was added followed by the addition of bis(triphenylphosphine)palladium dichloride (22.0 mg, 0.030 mmol), and the solution again bubbled with nitrogen. The reaction was then stirred at reflux for 3h, and then at 55 °C for 10 h. The reaction mixture was added to water (50 mL) and extracted with dichloromethane (2 × 50 mL). The organics were dried over magnesium sulfate, filtered, evaporated *in vacuo* and purified by flash chromatography (silica gel, eluting from 10% ethyl acetate:hexane to 40% ethyl acetate:hexane) to give the product and the hydrochloride salt was formed with HCl/ether to give the title compound as an off white solid (37.0 mg, 14%).

^{1}H NMR spectrum (CDCl$_3$): 2.40 (s, 3H); 2.50 (s, 3H); 3.75 (s, 2H); 3.80 (s, 2H); 3.85 (s, 3H); 7.00 (d, 2H); 7.10 (d, 1H); 7.25-7.70 (m, 6H); 8.10 (s, 1H); 8.30 (d, 2H).

Mass Spectrum: 396 [MH]+

Example K2: **<u>Preparation of *N*-(β-methylphenethyl)-*N*-Methyl-5-methyl-3-propargylamino-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine</u>**

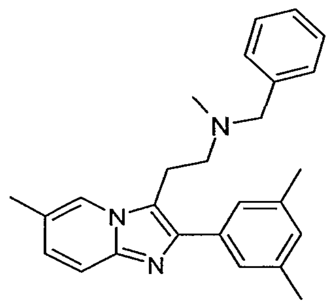


L-Deprenyl (592 mg, 3.16 mmol) was added to a solution of 5-methyl-3-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (500 mg, 1.58 mmol), and the reaction bubbled with nitrogen. Copper iodide (600 mg, 0.320 mmol) and bis(triphenylphosphine)palladium dichloride (110 mg, 0.160 mmol) were added, and the reaction stirred at reflux for 24h. The reaction mixture was partitioned between water (75 mL) and dichloromethane (75 mL), the organics extracted, dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography (silica gel, eluting with 30% EtOAc:Hexane to 80% EtOAc:Hexane) to give an oil. The hydrochloride salt was formed by addition of HCl/ether to give the title compound dihydrochloride as a yellow solid (63mg, 9%).

<u>^{1}H NMR spectrum (DMSO-d_6):</u> 1.20 (m, 3H); 2.40 (s, 3H); 2.75 (m, 1H); 2.95 (s, 3H); 3.45 (s, 2H); 3.80 (s, 3H); 4.70 (m, 2H); 7.00 (d, 2H); 7.20-7.65 (m, 7H); 8.20 (d, 2H); 8.70 (s, 1H).

<u>Mass Spectrum:</u> 424 [MH]+

Example L - Preparation of *N*-Benzyl-*N*-methyl-2-(3,5-dimethylphenyl)-3-ethylamino-5-methylimidazo[1,2-*a*]pyridine.



Step M1: 4-Chloro-2-bromopropyl-3,5-dimethylphenyl ketone.

Pyridinium tribromide (4.56 g 14.3 mmol) was added in one portion to a stirred solution of 4-chloropropyl-3,5-dimethylphenyl ketone (3.00 g 14.3 mmol) [synthesised as described in WO 98/55123] in CH_2Cl_2 (30 mL) at RT and the mixture stirred for 2h. The brown solution was then diluted with ether (200 mL) and washed with 20% NaS_2O_3 (aq) (150 mL), 2M HCl (200 mL) and brine (200 mL). The solution was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude title compound as a brown oil (4.11 g 99%).

Step M2: 2-(3,5-dimethylphenyl)-3-ethylamino-5-methylimidazo[1,2-*a*]pyridine.

A mixture of 2-amino-5-methylpyridine (1.08 g 10.0 mmol) and 4-Chloro-2-bromopropyl-3,5-dimethylphenyl ketone (2.90 g 10.0 mmol) in DMF (15 mL) was heated overnight at 80 °C. The mixture was partitioned EtOAc (50 mL) and saturated $NaHCO_3$ (150mL). The aqueous was extracted with EtOAc (5 × 25 mL) and the combined organics washed with water (25 mL) and brine (25 mL). The solution was dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatograpy (silica gel, slow gradient neat *iso*-hexanes to 50% EtOAc) gave the title compound as a yellow gum (610 mg 20%). HCl salt of title compound was prepared by the addition of 1.0M HCl in diethyl ether to a solution of the

title compound in EtOAc. The salt was precipitated with diethyl ether and collected by centrifuge.

Mass Spectrum: m/e $C_{18}H_{20}ClN_2$ (M+H) 299.16.
^{1}H NMR spectrum ($CDCl_3$): δ ^{1}H NMR (300 MHz) 2.33 - 2.50 (9H, m), 3.50 - 3.65 (2H, t); 3.70 - 3.80 (2H, t); 6.90 - 7.10 (2H, m); 7.36 (2H, s); 7.55 (1H, d); 7.70 - 7.85 (1H, m).

Step M2: *N*-Benzyl-*N*-methyl-2-(3,5-dimethylphenyl)-3-ethylamino-5-methylimidazo[1,2-*a*]pyridine.

N-Methyl-*N*-benzylamine (95 μL 0.737 mmol) was added in one portion to a stirred solution of 2-(3,5-dimethylphenyl)-3-ethylamino-5-methylimidazo[1,2-*a*]pyridine (200 mg 0.670 mmol) and di-isopropylethylamine (128 mL 0.736 mmol) in DMF (25 mL) was heated overnight at 100 °C. The mixture was partitioned EtOAc (2 × 50 mL) and saturated $NaHCO_3$ (250 mL) and the combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatograpy (silica gel, slow gradient neat iso-hexanes to 100% EtOAc) gave the title compound as a yellow gum (135 mg 44%). HCl salt of title compound was prepared by the addition of 1.0M HCl in diethyl ether to a solution of the title compound in EtOAc. The salt was precipitated with diethyl ether and collected by centrifuge.

Mass Spectrum: m/e (M+H) 384.67.
^{1}H NMR spectrum (DMSO-d_6 + CD_3COOD): δ ^{1}H NMR (300 MHz) 2.35 (6H, s), 2.75 (3H, s), 3.30 - 3.45 (2H, m); 3.65 - 3.85 (2H, m); 4.20 - 4.50 (2H, m), 7.20 (1H, s); 7.30 (2H, s); 7.35 - 7.45 (3H, m); 7.50 - 7.62 (2H, m); 7.70 - 7.85 (2H, m); 9.05 (1H, s).

THERAPEUTIC USES

Compounds of formula **I** are provided as medicaments for antagonising gonadotropin releasing hormone (GnRH) activity in men and women. To this end, a compound of formula **I** can be provided as part of a pharmaceutical formulation which also includes a pharmaceutically acceptable diluent or carrier (eg, water). The formulation may be in the form of tablets, capsules, granules, powders, syrups, emulsions (eg, lipid emulsions), suppositories, ointments, creams, drops, suspensions (eg, aqueous or oily suspensions) or solutions (eg, aqueous or oily solutions). If desired, the formulation may include one or more additional substances independently selected from stabilising agents, wetting agents, emulsifying agents, buffers, lactose, sialic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter and ethylene glycol.

The compound is preferably orally administered to a patient, but other routes of administration are possible, such as parenteral or rectal administration. For intravenous, subcutaneous or intramuscular administration, the patient may receive a daily dose of $0.1mgkg^{-1}$ to $30mgkg^{-1}$ (preferably, $5mgkg^{-1}$ to $20mgkg^{-1}$) of the compound, the compound being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively, the intravenous dose may be given by continuous infusion over a period of time. Alternatively, the patient may receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day. A suitable pharmaceutical formulation is one suitable for oral administration in unit dosage form, for example as a tablet or capsule, which contains between 10mg and 1g (preferably, 100 mg and 1g) of the compound of the invention.

The following illustrate representative pharmaceutical dosage forms containing a compound of the invention, or a pharmaceutically acceptable salt or solvate thereof (hereafter referred to as "compound X"), for use in humans.

(a)

Tablet I	mg/tablet
Compound X.	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

Buffers, pharmaceutically acceptable cosolvents (eg, polyethylene glycol, propylene glycol, glycerol or EtOH) or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

One aspect of the invention relates to the use of compounds according to the invention for reducing the secretion of LH and/or FSH by the pituitary gland of a patient. In this respect, the reduction may be by way of a reduction in biosynthesis of the LH and FSH and/or a reduction in the release of LH and FSH by the pituitary gland. Thus, compounds according to the invention can be used for therapeutically treating and/or preventing a sex hormone related condition in the patient. By "preventing" we mean reducing the patient's risk of contracting the condition. By "treating" we mean eradicating the condition or reducing its severity in the patient. Examples of sex hormone related conditions are: a sex hormone dependent cancer, benign prostatic hypertrophy, myoma of the uterus, endometriosis, polycystic ovarian disease, uterine fibroids, prostatauxe, myoma uteri, hirsutism and precocious puberty. Examples of sex hormone dependent cancers are: prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

ASSAYS

The ability of compounds according to the invention to act as antagonists of GnRH can be determined using the following *in vitro* assays.

Binding Assay Using Rat pituitary GnRH Receptor

The assay is performed as follows:-

1. Incubate crude plasma membranes prepared from rat pituitary tissues in a Tris.HCl buffer (pH. 7.5, 50 mM) containing bovine serum albumin (0.1%), [I-125]D-t-Bu-Ser6-Pro9-ethyl amide-GnRH, and the test compound. Incubation is at 4^{o}C for 90 minutes to 2 hours.

2. Rapidly filter and repeatedly wash through a glass fibre filter.

3. Determine the radioactivity of membrane bound radio-ligands using a gamma counter.

From this data, the IC_{50} of the test compound can be determined as the concentration of the compound required to inhibit radio-ligand binding to GnRH receptors by 50%.

Binding Assay Using Human GnRH Receptor

Crude membranes prepared from CHO cells expressing human GnRH receptors are sources for the GnRH receptor. The binding activity of compounds according to the invention can be determined as an IC_{50} which is the compound concentration required to inhibit the specific binding of [^{125}I]buserelin to GnRH receptors by 50%. [^{125}I]Buserelin (a peptide GnRH analogue) is used here as a radiolabelled ligand of the receptor.

Assay to Determine Inhibition of LH release

The LH release assay can be used to demonstrate antagonist activity of compounds, as demonstrated by a reduction in GnRH-induced LH release.

Preparation of Pituitary Glands

Pituitary glands obtained from rats are prepared as follows. Suitable rats are Wistar male rats (150-200g) which have been maintained at a constant temperature (eg, 25°C) on a 12 hour light/12 hour dark cycle. The rats are sacrificed by decapitation before the pituitary glands are aseptically removed to tube containing Hank's Balanced Salt Solution (HBSS). The glands are further processed by:-

1. Centrifugation at 250 x g for 5 minutes;
2. Aspiration of the HBSS solution;
3. Transfer of the glands to a petri dish before mincing with a scalpel;
4. Transfer of the minced tissue to a centrifuge tube by suspending the tissue three successive times in 10 ml aliquots of HBSS containing 0.2% collagenase and 0.2% hyaluronidase;
5. Cell dispersion by gentle stirring of the tissue suspension while the tube is kept in a water bath at 37°C;
6. Aspiration 20 to 30 times using a pipette, undigested pituitary fragments being allowed to settle for 3 to 5 minutes;
7. Aspiration of the suspended cells followed by centrifugation at 1200 x g for 5 minutes;
8. Resuspension of the cells in culture medium of DMEM containing 0.37% $NaHCO_3$, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids, 1% glutamine and 0.1% gentamycin;

9. Treatment of the undigested pituitary fragments 3 times with 30 ml aliquots of the collagenase and hyaluronidase;
10. Pooling of the cell suspensions and dilution to a concentration of 3 x 10^5 cells/ml;
11. Placing of 1.0ml of this suspension in each of a 24 well tray, with the cells being maintained in a humidified 5% CO_2/95% air atmosphere at 37°C for 3 to 4 days

Testing of Compounds

The test compound is dissolved in DMSO to a final concentration of 0.5% in the incubation medium.

1.5 hours prior to the assay, the cells are washed three times with DMEM containing 0.37% $NaHCO_3$, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids (100X), 1% glutamine (100X), 1% penicillin/streptomycin (10,000 units of each per ml) and 25 mM HEPES at pH 7.4. Immediately prior to the assay, the cells are again washed twice in this medium .

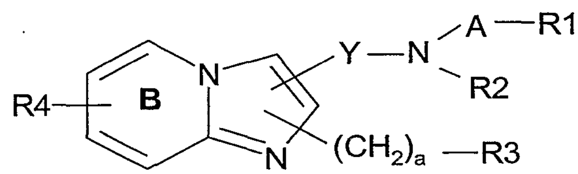
Following this, 1ml of fresh medium containing the test compound and 2nM GnRH is added to two wells. For other test compounds (where it is desired to test more than one compound), these are added to other respective duplicate wells. Incubation is then carried out at 37°C for three hours.

Following incubation, each well is analysed by removing the medium from the well and centrifuging the medium at 2000 x g for 15 minutes to remove any cellular material. The supernatant is removed and assayed for LH content using a double antibody radio-immuno assay. Comparison with a suitable control (no test compound) is used to determine whether the test compound reduces LH release. Compounds according to the present invention have activity at a concentration from 1nM to 30 μM.

CLAIMS

1. A compound of formula **I** or a pharmaceutically acceptable salt or solvate thereof

I



wherein:-

For R1 and R2, either:-

(i) R1= -C(X)NR5R6; -C(=NCN)NR5R6; -C(=CHNO$_2$)NR5R6; an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure containing from 1 to 5 heteroatoms independently selected from O, N and S; optionally substituted C1 to C8 alkyl; optionally substituted aryl; or optionally substituted aralkyl, where the alkyl moiety is C1 to C8;

R2 = H; optionally substituted C1 to C8 alkyl; optionally substituted aryl; optionally substituted aralkyl; -R7-R8, wherein R7 represents optionally substituted C1 to C8 alkyl and R8 represents an optionally substituted 5- to 10-membered mono- or bi-cyclic heterocyclic ring structure containing from 1 to 5 heteroatoms independently selected from O, N and S; optionally substituted C2 to C12 alkenyl; or optionally substituted alkenylaryl, wherein the alkenyl moiety is C2 to C12; and

A = a single bond; optionally substituted C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; or –R-Ar-R'-, where R and R' are independently selected from a bond, optionally substituted C1 to C8 alkylene and a C2 to C12 group having at least one alkene double bond; and Ar represents optionally substituted aryl; or

(ii) the structure N-R1R2 represents a 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S and optionally fused to a C5 to C10 ring structure, N-R1R2 being optionally substituted;

For R3 and R4, either R3 is selected from (iii) and R4 selected from (iv); or R3 is selected from (iv) and R4 selected from (iii):-

(iii) H; -ZR9, halogen; -ZC(O)NR9R10; -ZC(O)OR9; -ZC(O)SR9; -ZC(O)R9; C(R9)=N-OR10; -ZNR9C(O)NR10R11; -ZNR9SO_2R10; -ZSO_2R9R10; -ZCR9$(CN)_2$; -ZN(R9)CN; or an optionally substituted 3- to 6-membered heterocyclic ring containing from 1 to 3 heteroatoms independently selected from O, N and S;

(iv) -Z'-M, wherein
M represents a mono- or bi-cyclic aromatic ring structure optionally having at least one substituent selected from CN; NR12R13; an optionally substituted C1 to C8 alkyl; optionally substituted C1 to C8 alkoxy; halogen; $(CH_2)_b$-C(O)NR12R13; NR12-C(O)NR13R14; $(CH_2)_b$-SO_2NR12R13; NR12C(O)R13; NR12SO_2R13; $(CH_2)_b$OH; NR12CN; and CR12$(CN)_2$;

Wherein each R5, R6, R10, R11, R12, R13 and R14 is independently selected from H; optionally substituted C1 to C8 alkyl and optionally substituted aryl;

R9 is selected from H; optionally substituted C1 to C8 alkyl; optionally substituted aryl; -R-Ar, where R represents C1 to C8 alkylene and Ar represents optionally substituted aryl; and optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S;

X = O; S; or NR''', where R''' is H or C1 to C8 alkyl;

Y = a bond; C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; or a C2 to C12 group having at least one alkyne triple bond;

Z = a bond; C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; a C2 to C12 group having at least one alkyne triple bond; or -CR(R'), where R and R' are independently selected from H, CN, halogen, C1 to C8 alkyl, CH_2F, CHF_2, and C3 to C8 cycloalkyl;

Z' = a bond; C1 to C8 alkylene; a C2 to C12 group having at least one alkene double bond; a C2 to C12 group having at least one alkyne triple bond; or -CR(R'), where R and R' are independently selected from H, CN, halogen, C1 to C8 alkyl, CH_2F, CHF_2, and C3 to C8 cycloalkyl;

a = zero or an integer from 1 to 8;

each b independently represents zero or an integer from 1 to 8;

Wherein ring **B** is optionally further substituted.

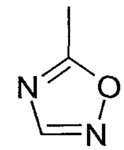
2. The compound of claim 1, wherein R1 is represented by option (i) and X represents S.

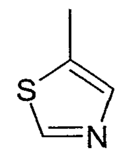
3. The compound of claim 1 or 2, wherein R1 is represented by option (i) and R5 and R6 each represent H.

4. The compound of claim 1, wherein R1 represents optionally substituted pyridyl.

5. The compound of claim 2, 3 or 4, wherein R2 represents hydrogen.

6. The compound of any preceding claim, wherein option (iii) represents NHC(O)NHR11; C(R9)=N-OR10, wherein R10 represents optionally substituted methyl; C(O)R9, wherein R9 represents optionally substituted phenyl; a substituent of formula **II,** optionally additionally substituted; or a substituent of formula **III,** optionally additionally substituted

II 

III 

7. The compound of any preceding claim, wherein for option (iv), the ring structure is phenyl.

8. The compound of any preceding claim, wherein for option (iv) the ring structure has at least one substituent selected from OH; $CONH_2$; CH_2CONH_2; $CH_2CONHCH_3$; $CH_2SO_2NHCH_3$; NHC(O)R13; $NHSO_2R13$; CH_2OH; NH-C(O)NH_2; NHCN; and $CH(CN)_2$.

9. The compound of any preceding claim, wherein R3 is selected from option (iv) and R4 is selected from option (iii).

10. The compound of any preceding claim, wherein Y represents CH_2 and a = zero.

11. The compound of claim 1, wherein the compound is selected from

N-Benzyl-*N*-methyl-2-(4-bromophenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(4-chlorophenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(4-fluorophenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(4-cyanophenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(4-methoxyphenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(3,4-dimethoxyphenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(3,4-dichlorophenyl)-3-methylamino-5-methylimidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(4-bromophenyl)-5-diethylamido-3-methylamino-imidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(4-bromophenyl)-5-isopropyloxycarbonyl-3-methylamino-imidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(4-isopropylamidophenyl)-5-isopropyloxycarbonyl-3-methylamino-imidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-methyl-2-(3,4,5-trimethylphenyl)-5-diethylamido-3-methylamino-imidazo[1,2-*a*]pyridine;

Ethyl *N*-benzyl-*N*-methyl-5-(3-acetamidophenyl)-3-methylamino-imidazo[1,2-*a*]pyridine-2-carboxylate;

N-Cyano-*N*'-[3-(1H-indol-5-yl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N*''-methyl-guanidine;

N-Cyano-*N*'-[3-(3,4-dimethoxyphenyl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N*''-methyl-guanidine;

N-Cyano-*N*'-[3-(4-chlorophenyl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N*''-methyl-guanidine;

N-Cyano-*N*'-[3-(3,5-dimethylphenyl)-imidazo[1,2-*a*]pyridin-2-ylmethyl]-*N*''-methyl-guanidine;

N,N-Dibenzyl-2-methylamino-3-(3,4-dimethoxyphenyl)imidazo[1,2-*a*]pyridine;

N,N-Dibenzyl-2-methylamino-3-(4-dimethoxyphenyl)imidazo[1,2-*a*]pyridine;

N-benzyl-*N*-methyl-2-methylamino-3-(4-chlorophenyl)imidazo[1,2-*a*]pyridine;

N-benzyl-*N*-methyl-2-methylamino-3-(3,5-dimethylphenyl)imidazo[1,2-*a*]pyridine;

N-Benzyl-5-bromo-3-(3-methylpropylamino)-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine;

N-Benzyl-*N*-Methyl-5-methyl-3-propargylamino-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine;

N-(β-methylphenethyl)-*N*-Methyl-5-methyl-3-propargylamino-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine; and

N-Benzyl-*N*-methyl-2-(3,5-dimethylphenyl)-3-ethylamino-5-methylimidazo[1,2-*a*]pyridine;

or a pharmaceutically acceptable salt or solvate thereof.

12. A compound according to any preceding claim for use as a medicament.

13. A pharmaceutical formulation comprising a compound according to any preceding claim and a pharmaceutically acceptable diluent or carrier.

14. Use of a compound according to any one of claims 1 to 11, in the manufacture of a composition, for antagonising gonadotropin releasing hormone activity.

15. Use of a compound according to any one of claims 1 to 11, in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinising hormone by the pituitary gland of the patient.

16. Use of a compound according to any one of claims 1 to 11, in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient.

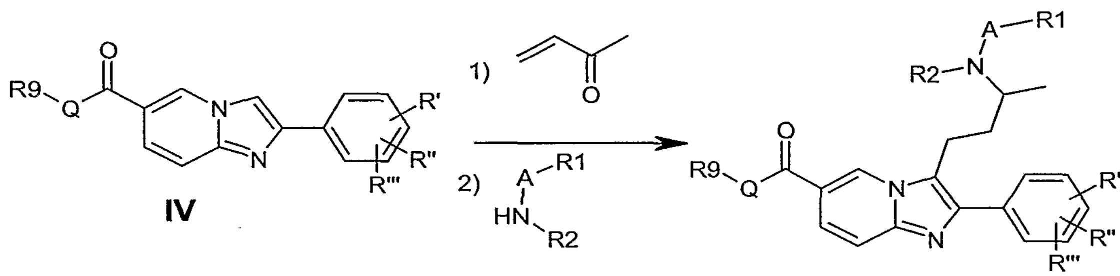
17. The use according to claim 16, wherein the sex hormone related condition is selected from a sex hormone dependent cancer, benign prostatic hypertrophy or myoma of the uterus.

18. The use according to claim 17, wherein the sex hormone dependent cancer is selected from prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

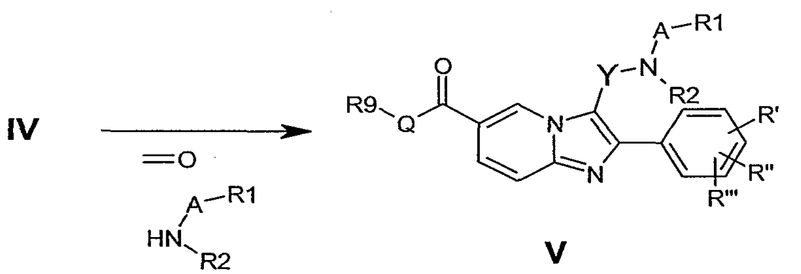
19. A method of antagonising gonadotropin releasing hormone activity in a patient, comprising administering to the patient a compound according to any one of claims 1 to 11.

20. A process of producing a compound according to any one of claims 1 to 11, wherein the process comprises a reaction step selected from steps (a) to (y):-

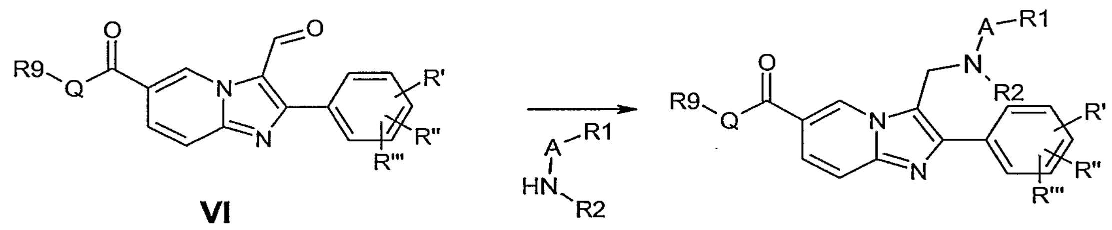
(a) Reaction of a compound of formula **IV** as follows



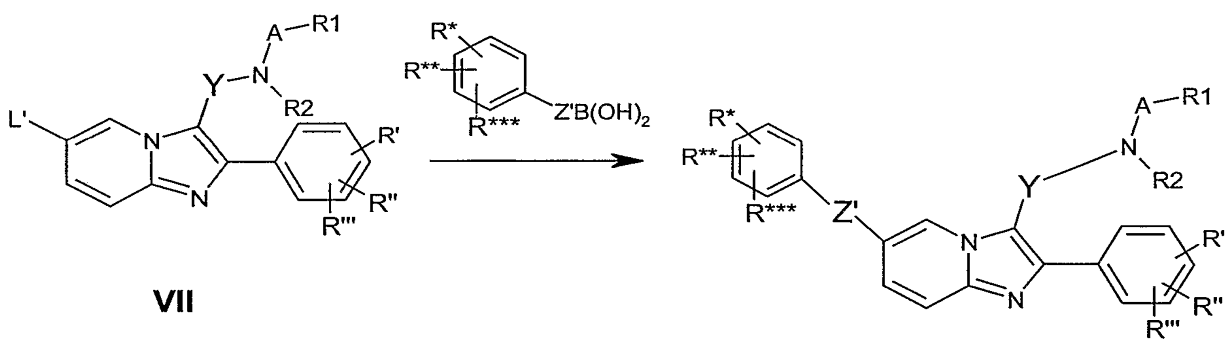
(b) Reaction of a compound of formula **IV** as follows



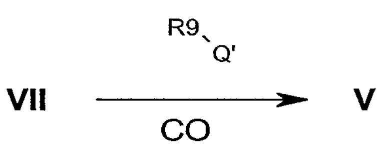
(c) Reaction of a compound of formula **VI** as follows



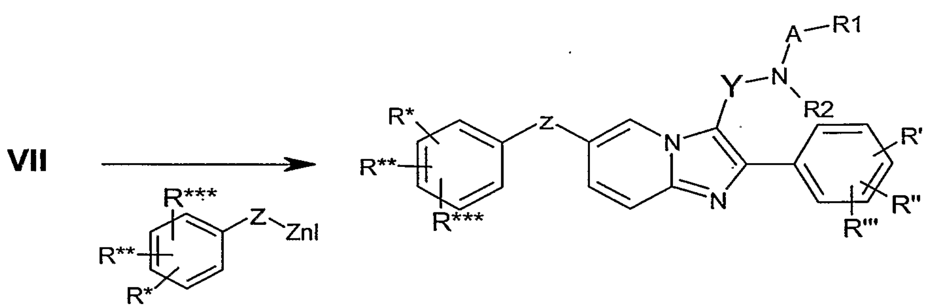
(d) Reaction of a compound of formula **VII** as follows



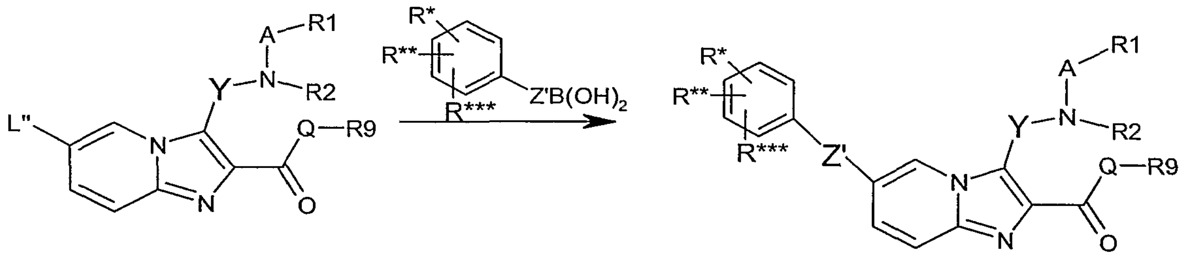
(e) Reaction of a compound of formula **VII** as follows



(f) Reaction of a compound of formula **VII** as follows

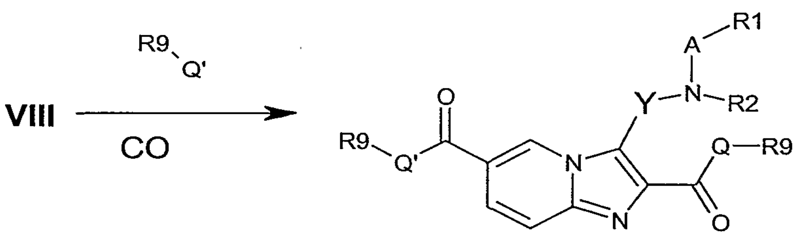


(g) Reaction of a compound of formula **VIII** as follows

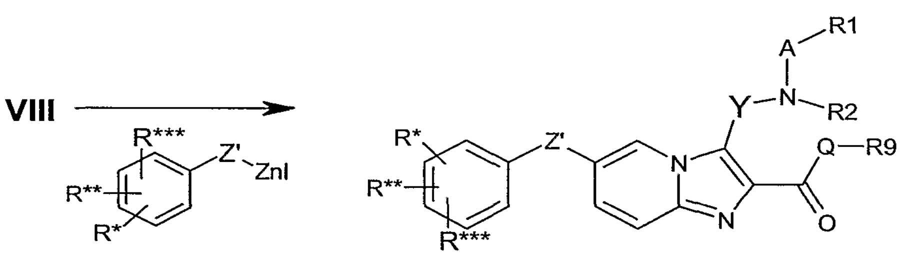


VIII

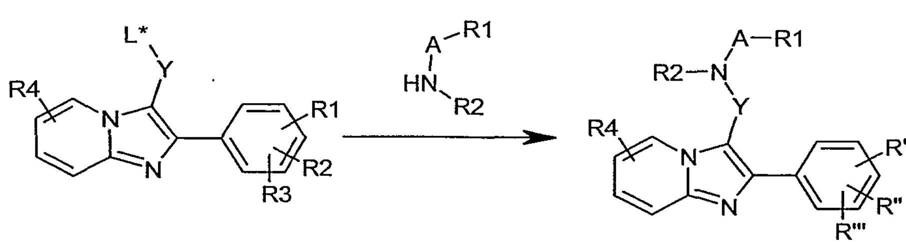
(h) Reaction of a compound of formula **VIII** as follows



(i) Reaction of a compound of formula **VIII** as follows

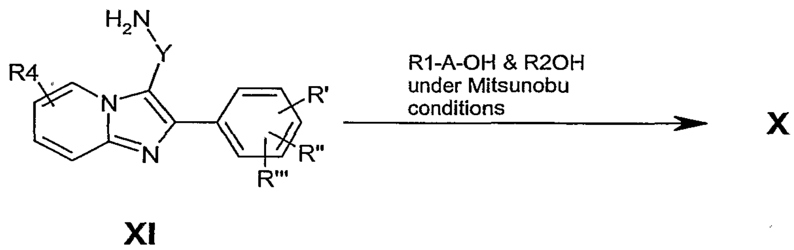


(j) Reaction of a compound of formula **IX** as follows

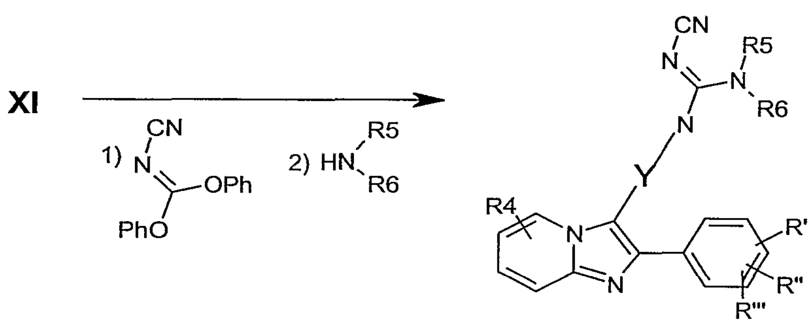


IX X

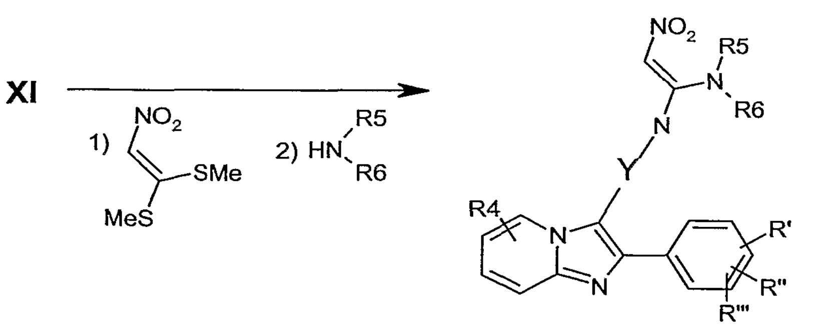
(k) Reaction of a compound of formula **XI** as follows



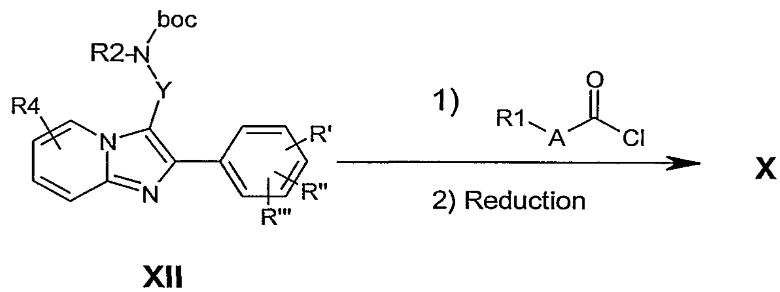
(l) Reaction of a compound of formula **XI** as follows



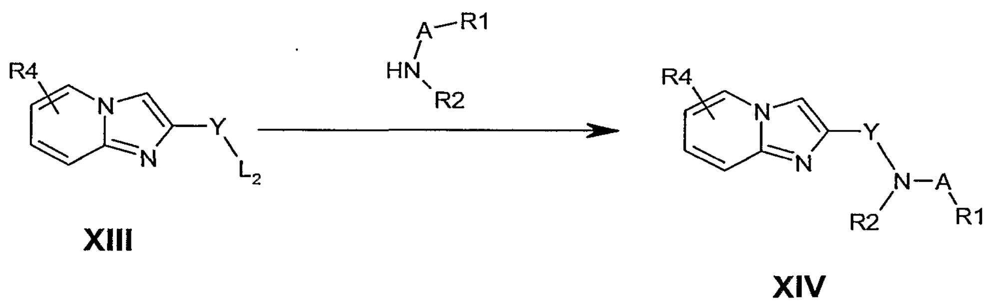
(m) Reaction of a compound of formula **XI** as follows



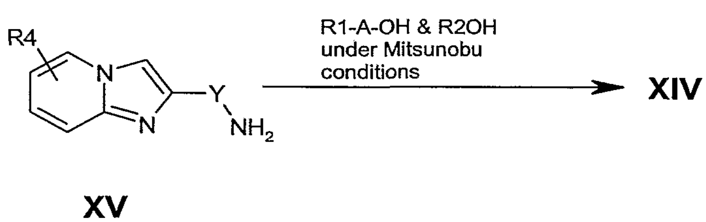
(n) Reaction of a compound of formula **XII** as follows



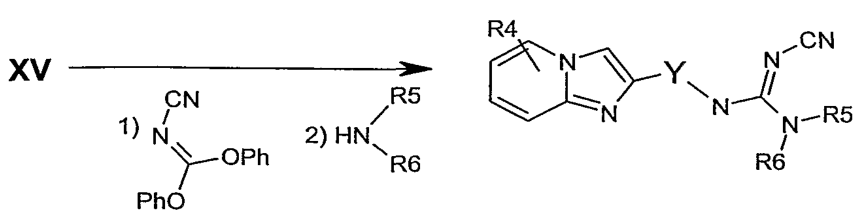
(o) Reaction of a compound of formula **XIII** as follows



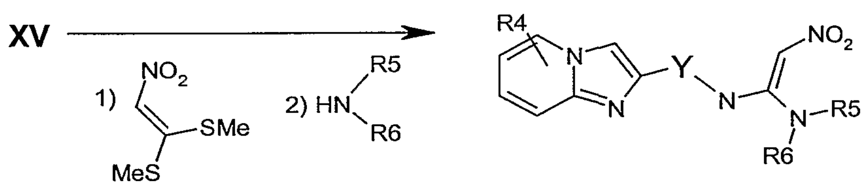
(p) Reaction of a compound of formula **XV** as follows



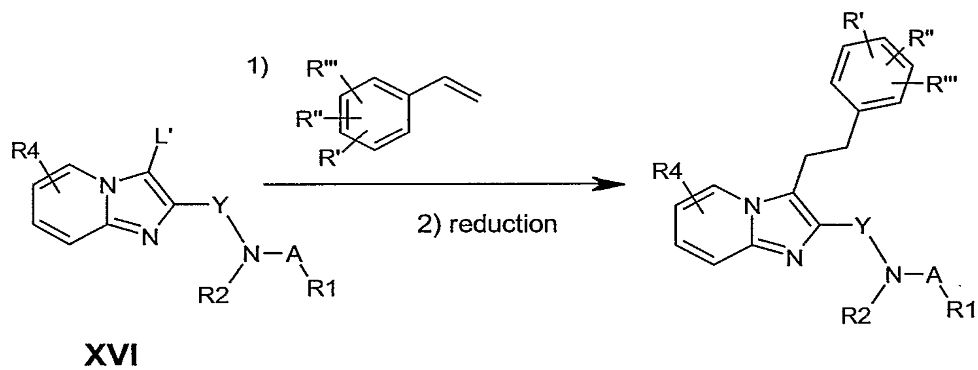
(q) Reaction of a compound of formula **XV** as follows



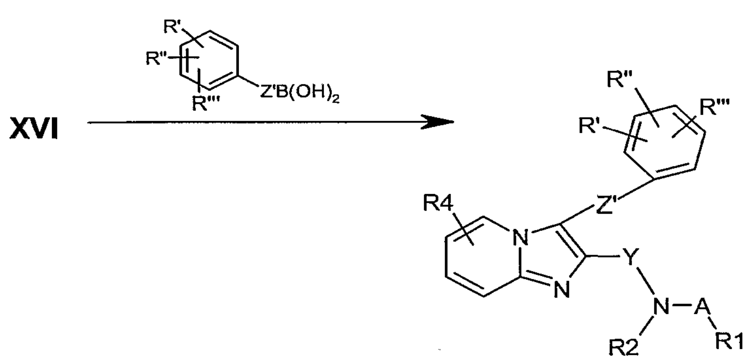
(r) Reaction of a compound of formula **XV** as follows



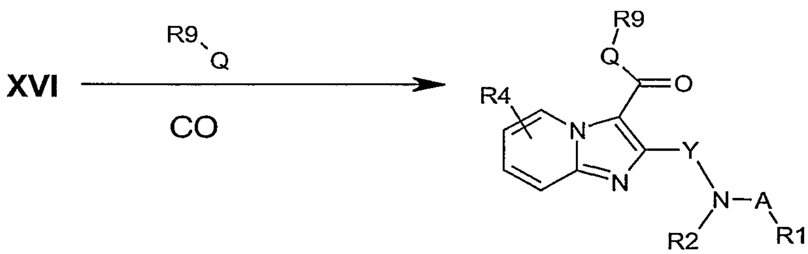
(s) Reaction of a compound of formula **XVI** as follows



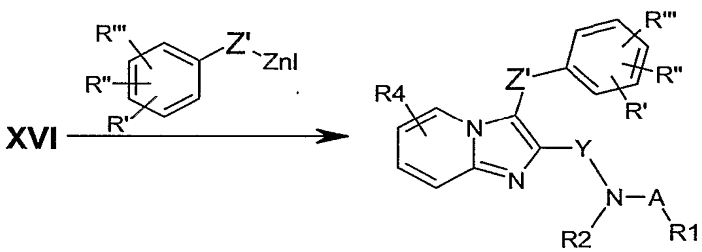
(t) Reaction of a compound of formula **XVI** as follows



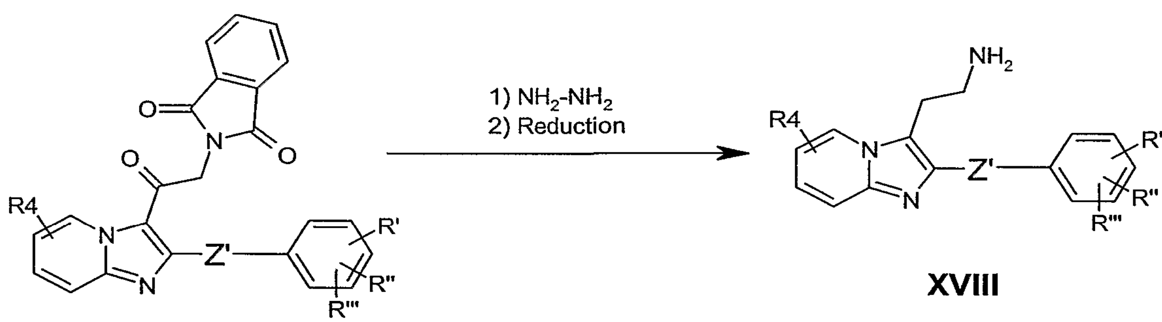
(u) Reaction of a compound of formula **XVI** as follows



(v) Reaction of a compound of formula **XVI** as follows



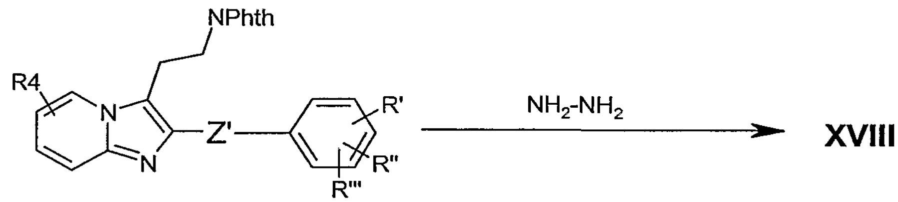
(w) Reaction of a compound of formula **XVII** as follows



XVII

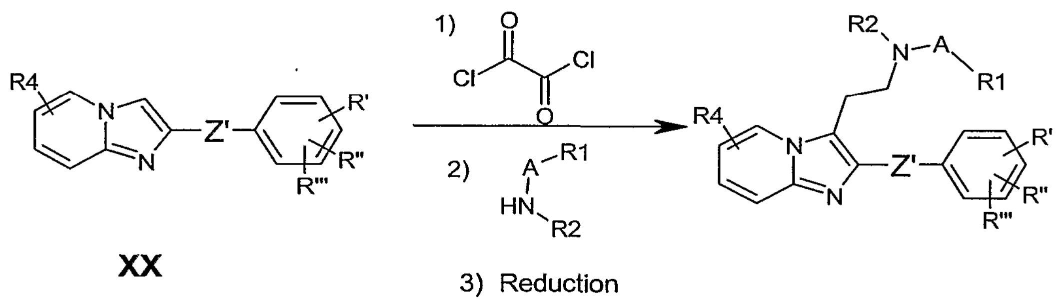
XVIII

(x) Reaction of a compound of formula **XIX** as follows



XIX

(y) Reaction of a compound of formula **XX** as follows



XX

Wherein R', R", R'", R*, R** and R*** are independently H or a substituent;

L', L'', L_2 and L* are leaving groups;

Q = NR10; S or O; and

Q' = NR10; S or O.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/00677

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 51596 A (GOULET MARK T ;MERCK & CO INC (US); WALSH THOMAS F (US); BUGIANESI) 14 October 1999 (1999-10-14) cited in the application page 3, line 22 -page 4, line 20; claims 1-28 ---	1-20
A	WO 00 53185 A (MERCK & CO INC ;WALSH THOMAS F (US); UJJAINWALLA FEROZE (US)) 14 September 2000 (2000-09-14) page 3, line 21 -page 4, line 18; claims 1-28; examples -----	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 April 2002	19/04/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schmid, A

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-10, 12-20 (all partly)

Present product claims 1-10, which are characterised by a great variability of substituents, relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found partly, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds according to the examples on pages 41-44 whereby the search has been based the heterocyclic core and the two substituents at the imidazol structure. The arguments are also valid for the claims 12-20.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

ıational Application No
ᴘᴄ ſ/GB 02/00677

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9951596	A	14-10-1999	AU	3367999	A	25-10-1999
			CA	2326140	A1	14-10-1999
			EP	1070064	A1	24-01-2001
			WO	9951596	A1	14-10-1999
			US	5985892	A	16-11-1999
WO 0053185	A	14-09-2000	AU	3514200	A	28-09-2000
			EP	1171135	A1	16-01-2002
			WO	0053185	A1	14-09-2000
			US	6288078	B1	11-09-2001